The New England
Journal of Medicine

Copyright, 1946, by the Massachusetts Medical Society

Volume 235 JULY 18, 1946 Number 3

# THE SURGERY OF THE INNOMINATE ARTERY*

GUSTAF E. LINDSKOG, M.D.†

NEW HAVEN, CONNECTICUT

THE first recorded operation on the innominate artery was performed by Valentine Mott of New York on May 11, 1818. Ligation of this vessel in an attempt to cure a traumatic subclavian aneurysm was followed by wound sepsis, secondary hemorrhage and death. Such was the fate of all subsequent surgical attempts in the preaseptic era until the twentieth recorded case, in which a successful ligation for subclavian aneurysm was performed on May 15, 1864, by Andrew Smyth,[1] of New Orleans. This patient was younger, and Fate was kinder. Recovery ensued after a terrifying series of hemorrhages, for the treatment of which metallic shot was repeatedly introduced into the suppurating wound. The eventual result was satisfactory, with arrest of symptoms until a recurrence and reoperation caused death eleven years later. Coppinger,[2] of Dublin, was the first European surgeon successfully to accomplish this formidable ligation. His operation was performed in 1893.

With the advent of antiseptic and finally aseptic technics and with the development of suitable anesthesia procedures, cases accumulated and relatively greater success was enjoyed. In 1905, Sheen[3] was able to collect 36 cases, including one of his own, which was the eighth successful ligation. In 1915, Thompson's[4] review added 16 cases. The latest complete survey of the literature was made by Greenough[5] in 1929. His report is characterized by accuracy and completeness. It comprises 91 cases and includes ligations, simple sutures, excisions and attempted ligations, besides reporting one personal success. In this series the operative mortality rate was 56 per cent; but in the most recent 25 cases it was only 16 per cent. I have re-examined the available literature and have collected 18 new cases, all of which have appeared since Greenough's summary.

## INDICATIONS FOR OPERATION

Ligation of the innominate artery has been performed for four indications: recent wounds of this vessel and its two major branches, 11 cases; traumatic aneurysm of the innominate, subclavian and carotid arteries, 20 cases; spontaneous — usually syphilitic — aneurysm of these vessels, 75 cases, and control of remote bleeding, 1 case. The indications and results are listed in Table 1. A certain latitude must be permitted in the interpretation of many of the operative reports. Some obscurity in description is comprehensible when one considers the inadequacies of anesthesia, lighting and exposure that hampered the earlier cases. Doubtless some fatal cases have never been reported in the literature, but probably few successful cases have so failed, so that the statistical results must be weighted on the favorable side.

TABLE 1. *Indications for and Results of Ligation of the Innominate Artery.*

| | No. of Cases | Recoveries | |
|---|---|---|---|
| | | No. | Percentage |
| Recent wounds: | | | |
| Innominate artery | 4 | 2 | |
| Subclavian artery | 3 | 0 | |
| Carotid artery | 4 | 1 | |
| Total | 11 | 3 | 27 |
| Traumatic aneurysm: | | | |
| Innominate artery | 5 | 4 | |
| Subclavian artery | 12 | 8 | |
| Carotid artery | 3 | 3 | |
| Total | 20 | 15 | 75 |
| Spontaneous aneurysm: | | | |
| Innominate artery | 30 | 15 | |
| Subclavian artery | 43 | 15 | |
| Carotid artery | 2 | 1 | |
| Total | 75 | 31 | 41 |
| Control of remote hemorrhage | 1 | 0 | 0 |
| Grand totals | 107 | 49 | |
| Percentage | | | 46 |

There can be no question of the propriety of and necessity for operation in traumatic lesions of the innominate artery and its bifurcation. The situation is urgent, and many of these patients do not survive the immediate injury, which is usually due to a gunshot, shrapnel or stab wound. A most interesting case of transverse rupture of the innominate artery with an intact chest has been reported.[6] This patient died without benefit of surgery, and the case is not included in the present series.

*Presented at the annual meeting of the New England Surgical Society, Boston, February 6, 1946.

†Associate professor of surgery, Yale University School of Medicine.

The problem of syphilitic or nonspecific aneurysm — hereafter called "spontaneous aneurysm" — calls for more detailed consideration and evaluation of data. Practically all these patients have had diffuse arterial and complicating visceral disease. They have an average age (forty-seven years) older than that (twenty-eight years), in the traumatic cases, and the danger of concomitant visceral complications is consequently greater. The incidence of therapeutic failure, especially after simple ligation, is higher in these cases than in the traumatic cases. Yet the life of a patient afflicted with such an aneurysm is usually a miserable one because of pressure symptoms, which include severe pain, dysphagia, hoarseness and dyspnea, and there is always the ominous threat of rupture into the pleural cavity or trachea or through the skin as a terminal event.

A few reported cases with small aneurysms in the third subclavian area, because of their small size and position, the presence of brachial pain and the absence of clinical syphilis, are reminiscent of aneurysm due to cervical rib. If so, they hardly constitute a proper indication for the operation as performed, since this type of case does not have a tendency to progression and is satisfactorily handled by local surgery.[7]

## Methods of Treatment

The ideal treatment of an aneurysm, whether traumatic or spontaneous, is either a Matas endaneurysmorrhaphy or proximodistal ligation and excision of the sac.[8] In the case of the innominate artery, the Matas operation does not lend itself to practical application, and there is no record of its deliberate use. Complete isolation and excision of the sac have been accomplished in only 3 cases, in all of which they were successful. Resort to the simpler procedure of ligation in continuity has been the rule, owing to technical difficulties or to the patient's condition. Proximal ligation of the innominate artery, with ligation of the carotid and subclavian arteries distal to the aneurysm — the so-called "triple operation" — has been performed more frequently than has radical excision, and the results have been better than those of proximal ligation alone.[4] Better surgical technic and more favorable operative conditions may have contributed to this difference.

In the case to be reported, a preliminary ligation of the common carotid artery was performed to test the cerebral circulation, promote the development of collaterals and prevent subsequent cerebral embolism or propagating thrombosis following direct operative trauma to the aneurysmal sac. Cerebral complications (Table 2) are reported to have caused postoperative death in 9 cases, and temporary disability in a few others. The average age in the fatal cerebral cases was 40.0 years, as compared with 42.5 years for the entire series. These facts suggest that the inherent vascular pattern is of more importance than the age factor.

Not a single case has been reported in which gangrene of the upper extremity followed ligation of the innominate artery, a fact that emphasizes the abundant collateral vascular pathways in the shoulder girdle and axilla (intercostal-subscapular). The occurrence of late ischemic pain, paresthesia and muscular weakness in the arm, however, has occasionally been noted and quite generally disregarded from the therapeutic standpoint. No mention has been made in recent years of the postoperative use of sympathetic block or dorsal sympathectomy. Although aneurysm of the innominate artery frequently produces Horner's syndrome on the right, there is recorded evidence in some cases that a sympathetic release with vasodilatation occurs in the vessels of the right upper extremity within twelve to twenty-four hours after operation. This phenomenon was noted in my patient, who has complained of no ischemic symptoms in the arm since operation.

Table 2. *Cause of Death.*

| Cause of Death | No. of Cases |
|---|---|
| Sepsis | 6 |
| Sepsis, with later hemorrhage | 14 |
| Late hemorrhage | 11 |
| Operative hemorrhage | 3 |
| Other operative accidents | 11 |
| Cerebral complications | 9 |
| Renal complications | 1 |
| Bronchopneumonia | 2 |
| Unstated | 1 |
| Total | 58 |

In view of the technical difficulties connected with exposure of the innominate artery and the high mortality in the earlier cases, various indirect or simpler therapeutic approaches for aneurysm of this artery have been devised and tried. One is the application of the wiring technic, which has been associated with uncertain results and with the complications pertaining to this method in other vessels.[9] A second is the technic of Brasdor-Guinar — namely, ligation of the subclavian and carotid arteries distal to the aneurysmal sac. With the use of this method, long-term cures of five to twenty-one years have been reported by Baldwin,[10] Schwyzer,[11] DaCosta (cited by Rundle[12]) and others. This procedure has been condemned by some authors, but analysis of the reports suggests that there is some prospect of relief or cure when a more radical approach is contraindicated by diffuse aortic disease, the patient's age or his general condition.

Finally, innominate aneurysm has been treated by the creation of an arteriovenous fistula between the common carotid artery and the jugular vein, with an end-to-end technic, as first suggested by Babcock. McCarthy[13] has reported 8 such cases,

TABLE 3. *Successful Cases of Ligation of Innominate Artery for Aneurysm.*

| SURGEON | YEAR REPORTED | YEAR OF OPERATION | SEX | AGE | PATHOLOGIC LESION | TYPE OF INCISION | ARTERY OR ARTERIES LIGATED | REMARKS | LAST REPORT |
|---|---|---|---|---|---|---|---|---|---|
| | | | | yr. | | | | | |
| Burrell (Greenough[5]) | 1895 | 1895 | M | 54 | Spontaneous aneurysm (subclavian and innominate) | Resection of portion of sternum | Innominate | Discharged from hospital on 73rd day; cardiac death on 104th day. | |
| Cuneo (Greenough[5]) | 1911 | 1905 | F | 49 | Spontaneous aneurysm (innominate and aortic) | Supraclavicular | Innominate | | Well in Dec., 1910 |
| Sargent (Greenough[5]) | 1911 | 1909 | F | 67 | Spontaneous aneurysm (bifurcation) | Resection of manubrium | Innominate and carotid | Transient hemiplegia on 10th day | Died in 1911 of nephritis and pneumonia; sac obliterated at autopsy. |
| Kimura (Greenough[5]) | 1913 | 1908 | M | 46 | Spontaneous aneurysm (bifurcation) | | Innominate, carotid and subclavian | Cured | Well in Apr., 1910 |
| Ballance (Greenough[5]) | 1918 | 1918 | F | 60 | Spontaneous aneurysm (innominate) (syphilitic) | | Innominate | | Died on June 5, 1921; sac occluded at autopsy. |
| Halsted (Greenough[5]) | 1926 | 1907 | M | 51 | Spontaneous aneurysm (bifurcation) | | Innominate artery (later band to carotid) | Pulsation ceased | Death from pneumonia on Jan. 1, 1908 |
| Lessnoi (Greenough[5]) | 1928 | 1914 | M | — | Traumatic aneurysm (innominate) | Supraclavicular | Innominate | Radial pulse returned before discharge | Well |
| Flint (Greenough[5]) | 1928 | 1927 | M | 37 | Traumatic aneurysm (bifurcation) | Excision of of manubrium | Innominate and subclavian | Aneurysmal sac packed | Well 5 mo. later; poor vision of right eye; husky voice. |
| Greenough (Greenough[5]) | 1929 | 1924 | F | 45 | Spontaneous aneurysm (bifurcation) | Sternoclavicular disarticulation | Innominate, carotid and subclavian | Wound sepsis | Well in Apr. 1925 |
| Miller, Dolbey and Ballance[18] | 1934 | 1925 | M | 54 | Spontaneous aneurysm (innominate) (positive serologic reaction) | Resection of clavicle and manubrium | Innominate | Subsequent ligation of carotid and subclavian arteries in 1925 | Recurrence with rupture and death in Oct., 1933 |
| Souttar[19] | 1934 | 1933 | F | 62 | Spontaneous aneurysm (innominate) (negative serologic reaction) | Supraclavicular | Innominate and subclavian | Traumatic hemiparesis at 7 mo. | Well |
| Rock (Rundle[12]) | 1937 | 1936 | F | 49 | Spontaneous aneurysm (innominate) (positive serologic reaction) | | Innominate, carotid and subclavian | | Living (with paresis) 3 yr. later |
| Edwards (Rundle[12]) | 1937 | 1935 | F | 64 | Spontaneous aneurysm (innominate) | | Innominate | Recurrence (see next case) | |
| Rock (Rundle[12]) | 1937 | 1936 | F | 64 | Recurrence (see previous case) | Sternotomy | Innominate, carotid and subclavian (excision of sac) | | Well in 1937 |
| Matas[9] | 1940 | Not stated | Not stated | Not stated | Spontaneous aneurysm (innominate) | | Innominate band | | Result not stated |
| | | Not stated | Not stated | Not stated | Spontaneous aneurysm (innominate) | | Innominate band | | Result not stated |
| Meade[20] | 1941 | 1936 | F | 65 | Spontaneous aneurysm (innominate and subclavian) (negative serologic reaction) | Supraclavicular | Carotid and subclavian (fascial strips) | Pulsation persisted | Improved |
| Elkin[15] | 1945 | 1945 | M | 25 | Traumatic arteriovenous aneurysm (innominate) | Resection of clavicle and manubrium | Innominate (also, right innominate vein) | | Well in May, 1945 |
| Lindskog | 1946 | 1945 | M | 27 | Traumatic aneurysm (innominate) | Section of clavicle and manubrium | Innominate | Preliminary carotid ligation | Well in 1946 |

all with positive serologic reactions at the time of operation. There were 2 operative deaths, one apparently due to anesthesia and the other to embolism, and 2 later deaths, one at five weeks from myocardial failure and the other at four weeks from rupture of the aneurysm. Four patients survived, 1 for more than four years, and 2 of them were able to resume work. These results and the generally recognized deleterious effect of a large arteriovenous fistula seem to make some other procedure a wiser choice.

### The Surgical Approach to the Innominate Artery

The earliest operations on the innominate artery were carried out through a cervical or supraclavicular muscle-cutting incision, of which the prosection or resection. A median section of the manubrium carried through to the second interspace, with section of the right clavicle in its medial third, gave an adequate exposure and a good functional result in my case. Elkin[15] has described the resection type of approach in detail.

In 107 reported cases of ligation or suture of the innominate artery, the immediate operative mortality was 54 per cent. Two of Greenough's cases are not included, since they represent incomplete attempts with survival. Since 1900 there have been reports of 61 cases, with 19 postoperative deaths, a mortality of 31 per cent. The principal causes of death are summarized in Table 2. It is evident that complications of wound sepsis, including mediastinitis, empyema, pneumonia and hemorrhage, have caused the largest group of fatalities. Acci-

Table 4. *Other Cases of Ligation of Innominate Artery for Aneurysm Since 1929.*

| Surgeon | Date of Report | Date of Operation | Sex | Age | Pathologic Lesion | Type of Incision | Artery or Arteries Ligated | Remarks | Result |
|---|---|---|---|---|---|---|---|---|---|
| | | | | yr. | | | | | |
| Chapman[21] ..... | 1929 | 1928 | M | 33 | Traumatic aneurysm (subclavian) | Section of clavicle | Innominate and carotid | Rupture of sac during excision; wound sepsis; empyema. | In good condition 6 mo. later |
| Lexer[16] ..... | 1934 | 1934 | M | 24 | Traumatic arteriovenous aneurysm (innominate) | Bilateral section of clavicle and resection of manubrium | Innominate (transvenous plication) also, ligated innominate vein | Streptococcal sepsis; pleurisy. | Death on 17th day |
| Turner (Rundle[12]) .. | 1937 | 1934 | M | 67 | Spontaneous aneurysm (innominate) (positive reaction serologic) | | Innominate (attempted) | Previous ligation of subclavian and carotid arteries in Jan., 1933 | Death from hemorrhage on 4th day |
| Matas[9] ..... | 1940 | Not stated | Not stated | Not stated | Spontaneous aneurysm (innominate) | | Innominate (metal band) | Hemorrhage and pulmonary complications | Death on 6th day |
| | | Not stated | Not stated | Not stated | Traumatic aneurysm (carotid) | | Innominate | Cerebral complications | Postoperative death, with hemorrhage |
| Brock[22] ..... | 1940 | 1939 | M | 66 | Spontaneous aneurysm (innominate and aortic) (syphilitic) | | Innominate | Wound sepsis and hemorrhage | Death 5 wk. later |
| Wheeler[23] ..... | 1942 | 1932 | M | 35 | Traumatic aneurysm (subclavian) | Section of clavicle and sternum | Innominate, carotid and subclavian | No pulsation after 4 mo. | Sudden death in Sept., 1940; cause unknown. |
| Langley[24] ..... | 1943 | 1943 | M | 23 | Shrapnel wound (innominate) | Section of clavicle | Innominate, carotid and subclavian | Shock, hemiplegia and pulmonary edema | Death in 16 hr. |

totype is Mott's. This has been adequate in some cases, particularly when the lesion was distal to the innominate artery and when the latter was at a high level.

The first mention of clavicular resection is in Cooper's case report cited by Greenough.[5] In 1895, Burrell[14] of Philadelphia first resected a portion of the sternum in this connection, and his patient survived ligation. It seems clear that adequate and safe exposure for surgery of the innominate artery demands some type of clavicular and manubrial

dents of technic follow in importance, after which come cerebral complications. Age appeared to have little or no relation to prognosis in this series, since the average stated age in the fatal cases was 42 years, whereas it was 43 years in the surviving cases.

### Arteriovenous Fistula

There are 3 recorded cases in which an arteriovenous fistula was treated by surgery of the innominate artery. Holman[8] in 1927 reported a case in which a subclavian arteriovenous aneurysm was

ruptured during dissection, necessitating ligation of the proximal innominate artery as an emergency procedure. The patient recovered and was apparently cured. Lexer's[16] patient had an aneurysmal varix of the innominate artery and left innominate vein following a stab wound. A transvenous arterial suture was performed, but death occurred from streptococcal sepsis. Elkin[15] in 1945 reported a case of fistula between the artery and both innominate veins. This fistula, which also followed a stab wound, was treated by ligation and section of the right innominate vein and double ligation of the artery. The patient made a good recovery.

No discussion of surgical procedures involving the innominate artery is complete without mention of the recent work of Blalock and Taussig.[17] In an attempt to increase the volume of pulmonary circulation in cases of congenital pulmonic atresia or stenosis, the normal innominate artery has been divided and the proximal end anastomosed to one of the pulmonary arteries.

## Case Report

A 27-year-old man was admitted by air transport to a United States naval hospital on August 30, 1945, with a chief complaint of severe pain in the right chest and swelling in the right side of the neck. On May 24, he had been injured by shrapnel from enemy air bombardment on Ie Shima, sustaining multiple small wounds of the right forearm, left foot and right shoulder and a small, sucking wound of the right supraclavicular region. He was rendered immediately unconscious but regained consciousness on the second day without major surgical intervention. He was aphonic for 10 days, had difficulty in vision for 1 week and noted a prominent mass in the lower right side of the neck. The voice improved gradually. On June 12, a bruit was discovered in the right supraclavicular region, and a roentgenogram of the chest showed an enlarged superior mediastinal shadow on the right side. On July 13, the patient had sudden, excruciating pain in the right side of the chest and neck, increased swelling of the mass and painful swallowing, even of liquids. This episode left a sequel of recurring severe pain in the substernal region and right shoulder and frequent headaches. The pain required a routine administration of morphine.

Physical examination on admission revealed a chronically ill man. The face and lips appeared slightly pale and cyanotic. The right palpebral fissure was narrowed, and the pupil was small. The voice was high pitched, and there was a paralysis of the right vocal cord. The trachea was deviated to the left because of a large visible and palpable mass deep in the supraclavicular and jugular region. The mass pulsated during systole, but there was no definite thrill or bruit. The carotid and radial pulses were palpable bilaterally and about equal in volume. Simultaneous brachial blood pressures were 116/80 on the right and 114/75 on the left. There were small healed wounds of the right wrist, right anterior deltoid region, right supraclavicular region and left foot. The direct measurements of venous pressures in the antecubital fossae were: right, 190 mm. of saline solution and left, 185 mm., with free respiratory excursions.

Laboratory studies revealed a negative Kahn reaction and a normal urine. The hemoglobin was 14.5 gm. per 100 cc., and the white-cell count 9000.

A roentgenogram of the chest demonstrated a diffuse widening of the superior mediastinal shadow, continuous with the ascending aorta. The trachea was narrowed and displaced toward the left. There was an irregular, radio-opaque foreign body in the left chest just above the aortic arch. A diagnosis of traumatic aneurysm of the innominate artery from a shrapnel wound was made.

Complete bed rest was enforced. Digital compression of the right carotid artery above the mass in the neck for 5 minutes hourly was begun on September 4. On September 19, ligation of the right common carotid artery was carried out just proximal to its bifurcation, under local anesthesia. This procedure resulted in a 3-day period of nausea and vomiting but no paresis of the left extremities and no change in blood pressure. On October 3, under intratracheal cyclopropane anesthesia, a trans-sternal anterior mediastinotomy was performed, with ligation of the proximal innominate artery. An incision was made with a horizontal arm just above and parallel to the median half of the clavicle, a vertical component over the midline sternum and a shorter horizontal component over the right 3rd costal cartilage. The proximal portion of the 2nd right costal cartilage was excised, the sternal body was rongeured slightly at this level, and the manubrium was split vertically with a Gigli saw introduced from above. The right clavicle was divided. By prolonged and difficult dissection in the densely scarred mediastinal connective tissue, the right and left innominate veins and superior vena cava were mobilized. Both had been displaced and flattened by a large fusiform dilatation of the innominate artery. By dissecting below and above the left innominate vein, a short but relatively normal proximal portion of this artery was freed and a braided linen umbilical tape was passed about it. Temporary occlusion of the vessel resulted in an obliteration of the right radial pulse. The ligature was secured, and a braided-silk ligature was placed above it. The chest was closed with wire sutures to the clavicle and sternum. A rubber-slip drain was left in the wound for 48 hours because of troublesome oozing, which had been particularly noticeable during the initial stages of the chest-wall incision.

Penicillin was given immediately after operation and continued during the 1st week. Early convalescence was complicated by restlessness, euphoria, disorientation, a rapid pulse and elevation of the systolic blood pressure to 150 or 170. The right arm and hand were cool and pale until the morning of the 2nd postoperative day, when warmth and superficial vasodilatation were observed. On the 3rd day, a loud, continuous murmur was heard in the pulmonic area and over the great vessels of the left neck, but only faintly on the right side. This gradually subsided and disappeared. The wound healed well.

A written communication from the patient in December, 1945, indicated continuing improvement, with complete relief of pain and sensations of pressure. There was still some nonpulsating fullness in the clavicular region.

## Summary

The literature on the subject of surgery of the innominate artery is reviewed, and the indications for and the technic and results of operation are discussed.

Eighteen cases have been added since a review by Greenough in 1929, and a total of 107 cases of ligation, excision or suture of the innominate artery, with an operative mortality of 54 per cent, are recorded.

Since 1900 there have been 61 cases, with a mortality of 31 per cent.

Nineteen cases of survival after surgery for innominate aneurysm, including the present case, are tabulated. A report of this case is presented.

789 Howard Avenue

## References

1. Smyth, A. W. Case of successful ligature of innominate artery. *New Orleans M. & S. J.* **22**:464-469, 1869.
2. Coppinger, C. Subclavian aneurysm. *Lancet* **2**:327, 1893.
3. Sheen, W. Of ligature of innominate artery: with report of successful case. *Ann. Surg.* **42**:1-32, 1905.
4. Thompson, J. E. Ligature of innominate artery for cure of subclavian aneurysm. *Ann. Surg.* **61**:641-657, 1915.
5. Greenough, J. Operations on innominate artery: report of successful ligation. *Arch. Surg.* **19**:1484-1544, 1929.
6. Feuz, J. Ein Fall von traumatischer Ruptur der Arteria anonyma. *Zentralbl. f. Chir.* **56**:3203-3205, 1929.
7. Lindskog, G. E., and Howes, E. L. Cervical rib associated with aneurysm of subclavian artery: report of case and review of recent literature. *Arch. Surg.* **34**:310-319, 1937.
8. Holman, E. Observations on surgery of large arteries: with report of case of ligation of innominate artery for varicose aneurysm of subclavian vessels. *Ann. Surg.* **85**:173-184, 1927.
9. Matas, R. Personal experiences in vascular surgery: statistical synopsis. *Ann. Surg.* **112**:802-839 1940.

10. Baldwin, J. F. Aneurysm of innominate, synchronous ligation of subclavian and common carotid with long survival: unusual incision. *Am. J. Surg.* 5:517, 1928.
11. Schwyzer, A. Aneurism of innominate artery. *Ann. Surg.* 96:666-669, 1932.
12. Rundle, F. Aneurysm of innominate artery treated by surgery: report of 3 cases and records of 22 cases collected from literature. *Brit. J. Surg.* 25:172-190, 1937.
13. McCarthy, P. A. Treatment of aneurysms of thoracic aorta and innominate artery by distal arterio-venous anastomosis. *Ann. Surg.* 91:161-196, 1930.
14. Burrell, H. L. Ligature of innominate artery, with report of case. *Tr. Am. S. A.* 13:291-312, 1895.
15. Elkin, D. C. Arteriovenous aneurysm: approach to innominate vessels. *J. A. M. A.* 129:26, 1945.
16. Lexer, E. Operation eines arteriell-venosen Anonyma-aneurysma. *Schweiz. med. Wchnschr.* 64:645, 1934.
17. Blalock, A., and Taussig, H. B. Surgical treatment of malformations of heart in which there is pulmonary stenosis or pulmonary atresia. *J. A. M. A.* 128:189-202, 1945.
18. Miller, C., Dolbey, R., and Ballance, C. Aneurysm of innominate artery: twenty-three years' history. *Lancet* 1:778-784, 1934.
19. Souttar, H. S. Aneurysm of innominate artery treated by proximal ligature. *Brit. M. J.* 1:1066-1068, 1934.
20. Meade, H. S. Compression of aneurysm of innominate artery with fascial straps. *Irish J. M. Sc.* April, 1941. P. 166.
21. Chapman, C. L. G. Ligature of innominate and common carotid arteries for subclavian aneurysm. *Brit. M. J.* 2:49, 1929.
22. Brock, R. C. Aneurysm of innominate artery: report of case treated surgically. *Guy's Hosp. Rep.* 90:180-195, 1940-41.
23. Wheeler, W. I. de C. Ligature of innominate artery for right subclavian aneurysm: end result. *Brit. M. J.* 2:422, 1942.
24. Langley, G. F. Gunshot wound of innominate artery. *Brit. M. J.* 2: 711, 1943.

# AN OUTLINE FOR THE TREATMENT OF SEVERE BURNS*

STANLEY M. LEVENSON, M.D.,† ROSS W. GREEN, M.D.,‡ AND CHARLES C. LUND, M.D.§

BOSTON

AT THE end of a three-year study of burns at the Boston City Hospital, the following outline of directions for their care has been prepared for the guidance of the hospital staff. This outline has been available at the hospital since July 1, 1945.

## DUTIES OF THE ACCIDENT–FLOOR PERSONNEL

Take temperature, pulse, blood pressure and respiration. Remove clothing and place patient on sterile sheet. Cover with sterile sheet.

Inspect area of burn and plot on a Boston City Hospital Burn Diagram.[2] Fill out diagram and make careful estimate of area burned. Order a normal dose of morphine if patient is conscious and in pain and not intoxicated.

Send to Shock Room if patient is in shock, if area is 25 per cent or more or if there is any sign of respiratory-tract injury, such as hoarseness, cough or dyspnea.

Send all other cases to operating floor.

Notify a surgical service concerning the case, giving *all* data found on examination above. All patients should be admitted to a surgical service except those with respiratory-tract injury only. The latter group should be admitted to a medical service.

Notify the Aural Service of all respiratory-tract injuries for aural consultation.

## DUTIES OF THE SURGICAL SERVICES

See patient at once. Shock may be expected shortly, if not already present, in cases of infants up to six years old with an 8 per cent burn or more and children and adults with a 15 per cent burn or more.

### *General*

(Occasional sick or very feeble patients may have shock with smaller burns.) All burns of these extents should have prompt intravenous treatment even if the temperature, pulse, respirations, blood pressure and hemoglobin level are normal. Do hemoglobin and urine examinations (catheterize if necessary). Repeat blood-pressure and pulse determinations every half-hour. Record all findings.

### *Shock*

Treat shock or give preventive treatment for shock *before* dressing the burn. Intravenous electrolyte should be started first, and in all cases in which the areas given above are involved plasma should be given simultaneously.

The electrolyte should consist of the following: 10 per cent dextrose in saline solution with the three following items added per liter: sodium bicarbonate, 3.75 gm. (put up in 50-cc. ampules); ascorbic acid, 1 gm.; and vitamin B complex,¶ 2 ampules. The amounts to be given are shown in Table 1. If the patient is intoxicated or in delirium tremens use five times this dose of ascorbic acid and of Vitamin B complex.

The first dose of plasma should be given rapidly and the first dose of electrolyte slowly unless the patient is in actual shock. If the usual peripheral veins are not accessible or are collapsed, the fluids should be given into the femoral vein, even if the groin region is burned.

It is essential to filter the plasma through sterile gauze just before using and give it through a Murphy drip set, to observe the rate of flow. The amounts to be given are shown in Table 1.

These doses may suffice for burns of 15 to 25 per cent in adults and of 8 to 15 per cent in infants who are not in shock, but in all cases of this severity or greater the systolic blood pressure and hemoglobin must be followed. If the patient goes into shock with the blood pressure below 70 at any time, the first dose of plasma should be repeated at once or a double dose given rapidly if none has been given. The second and subsequent hemoglobin values will indicate the need for further electrolyte and plasma in the severer cases. Do not give more electrolyte and plasma except for shock unless the hemoglobin has risen ten points or has gone above 110 per cent, whichever is reached first. The second and all subsequent doses of electrolyte and plasma

TABLE 1. *First Dose of Electrolyte and Plasma according to the Weight of the Patient.*

| WEIGHT | 10% DEXTROSE ELECTROLYTE IN SALINE SOLUTION | PLASMA |
|---|---|---|
| *lb.* | *cc.* | *cc.* |
| 150 or more | 1500 | 750 |
| 100–149 | 1000 | 500 |
| 50–99 | 500 | 250 |
| 35–49 | 250 | 250 |
| 20–34 | 150 | 150 |
| 5–19 | 5 per lb | 10 per lb. |

*From the Burn Assignment of the Surgical Service, the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine and the Department of Surgery, Harvard Medical School. The preparation of this paper for publication was aided by a grant from the John and Mary C. Markle Foundation.

The work described in this paper was done under a contract recommended by the Commitee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

†Research fellow in medicine, Harvard Medical School; research associate in surgery and resident fellow in medicine, Thorndike Memorial Laboratory, Boston City Hospital.

‡Formerly, assistant in surgery, Boston City Hospital.

§Assistant professor of surgery, Harvard Medical School; visiting surgeon, Boston City Hospital; formerly, member, Subcommittee on Burns, Division of Medical Sciences, National Research Council.

¶These ampules should contain in one ampule 10 mg. of thiamin, 4-10 mg. of riboflavin, 50-250 mg. of niacinamide, 5-10 mg. of pyridoxine and 5-50 mg. of pantothenic acid. Among the preparations meeting these standards are Betalin Complex (Lilly), Solu-B (Upjohn) and Betasynplex (Winthrop).

should be given as outlined in Table 2. Use 10 per cent dextrose in *distilled water* instead of *saline solution* during the remainder of the first twenty-four hours.

Further doses are to be given if indicated by further rises in hemoglobin. If further intravenous treatment is needed for shock after an amount of 10 per cent dextrose in distilled water has been given equal to the original dose

TABLE 2. *Subsequent Amounts of Electrolyte and Plasma to be Given for Each Point Rise in Hemoglobin or for Each Point It Is above 100 Per Cent according to the Weight of the Patient.*

| WEIGHT | 10% DEXTROSE ELECTROLYTE IN DISTILLED WATER | PLASMA |
|---|---|---|
| *lb.* | *cc.* | *cc.* |
| 150 or more | 50 | 50 |
| 100–149 | 35 | 35 |
| 50–99 | 20 | 20 |
| 35–49 | 15 | 15 |
| 20–34 | 10 | 10 |
| 5–19 | 0.5 per lb. | 0.5 per lb. |

of saline solution, give only plasma. Severe burns may need about 1000 cc. of plasma for each 10 per cent area of burn up to a maximum of 5000 cc. in twenty-four hours.†

The blood pressure determinations should be continued every half-hour for twenty-four hours, the hemoglobin every two hours until stabilized, and the temperature and respiration every two hours. Children under six should have a rectal temperature every hour.

*Dressing*

A dressing should be applied as early as is consistent with the patient's condition. It should not be started until shock is relieved or until preventive treatment for shock has been started. The intern or resident doing the dressing must be scrubbed, gowned, capped and masked. If the dressing is difficult (25 per cent area or more or a restless or delirious patient), there must also be a scrubbed assistant. The patient should be placed on a sterile sheet and the adherent clothing removed. Blisters must not be cut or broken, and no attempt should be made to wash or clean off any dirt of any kind. A pressure dressing should be applied. Casts may be applied to extremities on direction of a visiting surgeon. The only exceptions to the above are in the cases of the face, neck, anus and genitalia, which should be covered with a thick layer of sterile vaseline and one layer of fine mesh gauze, and nothing else. Provision should be made for replacing these frequently on the ward.

*Technic of Pressure Dressing*

Under operating-room conditions, fine meshed gauze, dry, should be applied directly to the wound surface. Over this, sufficient Surgine* should be wrapped to make possible even compression by means of an elastic bandage. (The final dressing after compression should be about 2.5 cm. thick.) It should be emphasized that to be maximally effective the dressing should be applied as soon as permitted by the general condition of the patient, since the greatest amount of swelling occurs in the first few hours following injury. Also, since the swelling is not limited to the burned areas but occurs also in the immediately adjacent areas, these areas must be incorporated in the dressing. In burns of the extremities the dressing must extend distally to cover completely the hand and foot, even if these areas are not burned; otherwise, the venous return from these areas will be obstructed, and as the back pressure builds up, the arterial blood supply will be impaired. In certain cases where these precautions have not been taken dressings have had to be removed because of impending gangrene. Elevation of an extremity, with a properly applied dressing, may help prevent stasis and discomfort. In applying a pressure dressing the tension must be uniform, and care must be taken that no more pressure is used than required. In burns of the chest and abdomen a pressure dressing, as such, cannot be applied without interfering with the patient's breathing; under these circumstances a firm bulky dressing without pressure is used. The initial dressing is left in place for about fourteen days. At the end of this time superficial second-degree burns are healed, while deep burns are beginning to slough.

*Post-Dressing Care*

Order patient sent to the ward only when well out of shock.

Order morphine in *small doses.*

Order pulse, respiration and blood-pressure determinations every half-hour.

Order hemoglobin determinations every two hours.

Order temperature determinations every two hours, or every hour (rectal) up to six years old.

Order report of any fall in blood pressure of 20 points or below 90 systolic, any rise in pulse of 30 points or above 120, any rise in respiration above 30 and any rise in temperature to or above 103°F. or any chill or other unfavorable symptom.

*Post-Dressing Shock*

The treatment of this should be mainly by plasma and electrolyte, as directed above. The best sign that shock is fully relieved is a good flow of urine. Be careful of giving too much fluid, especially to very young or very old patients.

*Kidney Function*

Impairment of kidney function is one of the important early complications of the severely burned patient. To determine the kidney function, urine specimens are necessary; therefore, put all patients with burns of 25 per cent or greater on constant drainage for the first few days. The important etiologic factors of reduced renal function appear to be shock and hemoglobinuria. Every effort must be made to prevent the occurrence of shock or, if shock is present, to combat it vigorously and immediately. Hemoglobinuria is the result of marked hemoglobinemia, which in turn results from injury to the circulating red cells by heat at the time of burning. From analogy with hemolytic blood-transfusion reactions, prompt and continued alkalinization of the urine during the period of hemoglobinemia (usually forty-eight to seventy-two hours) should be made. This can be accomplished initially by the intravenous injection of an ampule of sodium bicarbonate, in addition to that already recommended in the section on the treatment of shock. Later, additional bicarbonate should be given only if the urine fails to become or to remain alkaline.

Daily intake and output records should be kept for at least the first week in all patients with burns of 10 per cent or greater, and as much longer as is indicated in patients showing any impairment of renal function. An attempt should be made to keep the urine output between 1000 and 1500 cc. daily. Fluids during the first day should be given as outlined previously. If thereafter the oral intake is insufficient, it should be supplemented by intravenous fluids or by clysis. No more than 1500 cc. of the supplemental fluids should be electrolyte. In cases with marked oliguria or anuria, care should be taken not to overload the patient, particularly with sodium salts. Plasma protein, nonprotein nitrogen, carbon dioxide, chloride and routine urine determinations should be frequently done.

*Hyperpyrexia*

Patients with burns frequently have a period of high temperature (up to 109°F.) in the first two days after the burn, and not infrequently at much later dates. This is likelier if shock has been poorly treated but can occur without any shock. It is not necessarily the result of infection or of pyrogens in the intravenous fluids.

The patient with a burn does not tolerate a high temperature and will die if it remains at or above 105°F. for a few hours. In most cases this fever may be brought down by energetic treatment given *at once.* If the fluids given have not been according to the above standards, more fluid will help, but main attention should be paid to ice-water sponge baths to all exposed skin. If less than 50 per cent of skin is exposed, it may be necessary to remove some of the dressings. Open windows, create a draft, strip off all bedclothes and make an ice-water bath in the pa-

*Surgine is the name of a composite cotton dressing material used in many hospitals for abdominal pads. Large sterilized rolls of this material are convenient for dressing large burns.

†Whole blood has recently been found to be at least as useful as plasma in the prevention of burn shock. When whole blood is used in large quantities, the hematocrit and hemoglobin values are unreliable indicators of blood volume.

tient's bed and keep sponging him for half an hour or more if necessary to bring the temperature down to 102°F. Heated cradles are not to be used at any time in the care of burns. Heavy blankets are to be used only temporarily during a chill or when the room is extremely cold.

*Respiratory-Tract Injury*

Respiratory-tract injury is a serious complication of burns. Its presence should be suspected in any patient with flame burns of the face (even minor), particularly if he gives a story of inhaling large quantities of smoke and so forth or having lost consciousness. An aural consultation should be obtained immediately on such patients, particular attention being paid to the epiglottis and vocal cords. The room should be humidified, and a tracheotomy set should be kept at the patient's bedside. Respirations should be checked every half-hour. If any hoarseness, dyspnea or stridor occurs, the patient should be placed in an oxygen tent. If there is evidence of bronchial spasm, aminophyllin intravenously or adrenalin or ephedrin by nebulizer should be tried. If signs of laryngeal obstruction develop, immediate tracheotomy must be done. Suction through the tracheal tube should be carried out when needed. An aural consultant should be on hand to perform bronchoscopic aspiration if further obstruction develops. All personnel coming in contact with the patient should be masked.

*Sedation.* Restlessness may be due primarily to oxygen lack, in which case measures to increase oxygen supply as outlined above should be carried out, to pain (from surface burns), in which case Demerol, rather than morphine, should be used, or to fear and nervousness, in which case barbiturates are indicated.

*Chemotherapy.* Parenteral penicillin, 25,000 units intramuscularly every three hours, should be started on entry. If the urine output is good, sulfadiazine in full doses may also be given.

*Local measures.* If burns of the nose and pharynx are present, the patient may be made more comfortable by swabbing the nose with a bland oil and having him gargle with a soothing mixture, such as dextrose in water.

*Anemia*

After the second day anemia may be troublesome. Make hemoglobin determinations daily until stabilized, and then weekly until discharged. Give whole-blood or red-blood cells in sufficient amounts to keep the hemoglobin at 90 per cent. Any level below 80 per cent should be corrected at once.

*Nutrition*

Loss of weight, often marked, has long been recognized as a serious complication in severely burned patients.

The estimation of the status of a burn patient with regard to the presence or degree of nutritional deficiency is not simple. The factors necessary for a critical evaluation are the optimum weight of the patient, the observed weight of the patient, the plasma protein level, the plasma albumin level, the plasma volume, the nitrogen intake and the nitrogen output. Actually, main reliance in clinical work has to be placed on a nutritional history, on the patient's weight and on serum protein determinations.

The weights of these patients may be secured at each dressing change by putting the patient, covered with a sterile sheet but with the dressings removed, on a weighed stretcher, each end of which is placed on a scale. Slight changes of weight are often the first indication that the patient's nutritional condition is getting better or worse.

The food provided must be an adequate metabolic mixture containing, in addition to adequate amounts of protein, sufficient calories, fat, carbohydrate, minerals, water and accessory food substances. As seen in Table 3, the minimum essential needs for protein, calories and vitamins are as great as or greater than the need for these items in an illness of any kind. This table is to be followed for adults and for children weighing 50 pounds and over. Reduce by 25 per cent from thirty to forty-nine pounds, and by 50 per cent from fifteen to twenty-nine pounds. Under fifteen pounds give 125 per cent, 150 per cent, 200 per cent and 300 per cent, respectively, of normal proteins and calories for 1–4, 5–9, 10–19 and 20+ per cent burns. Give 25 per cent of vitamins indicated for the area in above table to these infants.

Additional vitamins from liver and yeast are helpful. Severe cases should be given up to 30 gm. of yeast a day. Liver may be given in the form of liver extract.

Whenever possible, protein losses or deficiencies should be corrected by oral feeding. It is not enough for the surgeon to order a high-protein, high-calorie, high-vitamin diet. If such a diet is ordered, the patient may fail to benefit from the order for any one of the following reasons. The diet presented to the patient is not as specified. The diet presented is not eaten in whole or in part because it lacks palatability, there is lack of appetite, and there is a lack of nurses to encourage eating. Food eaten may be partly or wholly lost because of diarrhea or vomiting.

TABLE 3. *A Minimum Food Needed Daily by Patients with Burns, according to Total Area Unhealed.*

| Burn Area | Protein | Calories | Ascorbic Acid | Thiamin | Ribo-flavin | Nicotin-amide |
|---|---|---|---|---|---|---|
| % | gm. | | gm. | mg. | mg. | mg. |
| 20 | 300–400 | 5000 | 2.0 | 50 | 50 | 500 |
| 10–19 | 200 | 3500 | 1.0 | 25 | 25 | 200 |
| 5–9 | 125 | 3000 | 0.5 | 15 | 15 | 100 |
| 1–4 | 90 | 2500 | 0.5 | 10 | 10 | 50 |

These difficulties have been frequently encountered in caring for patients with burns during the last two years. The fact that the first item is mentioned may be a surprise. What especially happens in these days with the shortage of nurses is that there are frequent times when supplementary feedings are not brought to the patient because the nurse has other duties to perform that she thinks are more important or more urgent. This is particularly likely to happen at night.

The three items listed under the second item are interrelated. It is a common experience to find that a sick patient has no appetite. If, however, special attention is paid to the likes and dislikes of the patient and special or other nurses are available to encourage eating and to offer meals when the patient desires them instead of only at stated routine times, many such patients will eat a surprisingly large amount of food.

The two items under the third item are also related to each other. Forcing the diet on a sick patient does not always result in a net gain. Nausea, vomiting, distention and diarrhea, singly or together, are limiting factors. In general, the sicker the patient is the less fat is tolerated and the larger the proportion of protein should be. It has been found that at least 25 per cent of the calories in the diet should come from protein and not over 15 per cent from fat if any of these intestinal symptoms have recently occurred. It is well to take a number of days to increase the food intake, since sudden increases are likelier to be followed by gastrointestinal symptoms, which can usually be avoided by more cautious increases. If this diet is not tolerated, protein in the form of a digest should be tried and will frequently be well tolerated. The available digests are not particularly palatable and should generally be given by intubation.

Intubation feeding is important and may be used to increase greatly the intake of food. Medium-caliber nasal stomach tubes are used and left in all the time or for many hours a day. If left in continuously, the tube should be removed every third or fourth day for cleaning. About 200 cc. of fluid may be given at a time, spaced between meals and at night, but there is a wide variation in the amount and frequency of supplementary tube feedings that different patients can take. It is well to start with a mixture of half skim milk and half water or one of protein hydrolysate and carbohydrates. Instead of supplying the mixture in intermittent doses, a drip apparatus may be used that can, after a short period of training, be regulated by some patients themselves. If 125 to 150 gm. of protein and 2000 to 2500 calories are given by intubation in addition to an average house diet, the patient should receive a total of about 200 gm. of protein and over 4000 calories. Usually, however, the patients who are

given forced supplementary feeding will not take the whole of their house diet in addition.

In certain patients needing only moderately high diets and in nearly all those needing 300 gm. of protein or sugar, it may be impossible to furnish the required foodstuffs by the oral or gavage route. In these cases supplemental intravenous feedings are indicated. Intravenous feedings are also indicated in cases of disturbed gastrointestinal function, either primary or secondary to nutritional disturbance. In the latter cases there may be surprising improvement in gastrointestinal function after intravenous alimentation.

Parenteral feeding should be continued as a supplement until oral feeding, with or without gavage, has been established at a sufficient level not only to maintain the patient in nutritional equilibrium but also to restore at a rapid rate all tissues that have been depleted. Up to 225 gm. of protein equivalent have been given in twenty-four hours in the form of an acid hydrolysate of casein (Parenamine) or an enzymatic hydrolysate of casein and pancreas (Amigen). The suggestion of Butler and Talbot[2] for increasing the value of intravenous protein hydrolysates by adding dextrose has been successfully followed. By adding 300 cc. of 50 per cent dextrose to 1000 cc. of Amigen, there is obtained 1300 cc. of a solution composed of 4 per cent hydrolysate and 15 per cent dextrose, which represents 50 gm. of protein and 1000 calories. This quantity can be given into a large vein with a 20-gauge to 21-gauge needle in four hours, without much danger of thrombosis of the vein and can be repeated three times a day. The speed of administration is limited by the amount of dextrose present, the ratio of dextrose administration not exceeding 0.8 gm. per kilogram of body weight per hour. Administration at a faster rate produces glycosuria and excessive diuresis. Nausea may be caused if the enzymatic hydrolysate is introduced too rapidly, and thrombosis of the vein used for the injection may occur with the acid hydrolysate.

In late stages of severe burns, testosterone propionate should be given in doses of 25 mg. intramuscularly every other day to increase the positive nitrogen balance by reducing the loss of nitrogen in the urine.

*Subsequent Dressings and Grafts*

These should be done infrequently, about ten to fourteen days apart, and in the operating room under strict asepsis. The dressings should be large, bulky and firm. Until some antiseptic of value is found, no ointments and no chemicals should be used except on the face, neck, genitalia and anus. The ointment dressings on these areas alone should be done whenever necessary, and therefore frequently, on the ward. Skin grafts should be placed on all deep burns at the earliest possible time. Frequent dressings and surface antiseptics are not needed and should not be used before grafting. The dressings outlined above are the best possible preparation for grafting. If hemolytic streptococci are found, intramuscular penicillin should be used before and after grafting in doses of 20,000 units every two hours. In the absence of the streptococcus penicillin is not necessary. Dermatome grafts should be employed whenever possible. When general anesthesia is needed for grafting or for dressings the anesthetic of choice is cyclopropane.

### Nursing Care

Even in spite of carrying out every item in this outline, the fact remains that a patient with a deep burn of 5 per cent or more can be saved only if special nursing care is given. This is not at present provided on the wards of many hospitals unless special nurses are available. Any patient with an unhealed deep burn of 20 per cent or more needs three nurses a day; with one of 10 to 19 per cent, two periods of special nursing a day are needed; and with one of 5 to 9 per cent, one period of special nursing a day is needed.

A full discussion of the present status of the treatment of burns has been published and explains the reasons for the directions given here.[3]

### References

1. Lund, C. C., and Browder, N. C. Estimation of areas of burns. *Surg., Gynec. & Obst.* 79:352-358, 1944.
2. Butler, A. M., and Talbot, N. B. Parenteral-fluid therapy. II. Estimation of losses incident to starvation and dehydration with acidosis or alkalosis and provision of repair therapy. *New Eng. J. Med.* 231: 621-628, 1944.
3. Lund, C. C., Green, R. W., Taylor, F. H. L., and Levenson, S. M. Burns: collective review. *Surg., Gynec. & Obst.* 82:443-478, 1946.

# EFFERVESCENT MIXTURES AS ADJUVANTS TO THE RAPID ABSORPTION OF INGESTED DRUGS*

GIORGIO LOLLI, M.D.,† AND RUTH SMITH, B.A.‡

NEW HAVEN, CONNECTICUT

ALTHOUGH there are many and obvious advantages to the oral administration of drugs, there are certain equally obvious disadvantages. Of these the most prominent are the uncertain and variable rate of absorption and gastric irritation. It is probable that when irritation occurs, its intensity varies with the duration of the contact of the drug with the gastric mucosa, and that it is least when emptying of the stomach is rapid. Since few drugs are absorbed directly from the stomach, the rate of emptying affects the speed of therapeutic response, and for drugs whose action depends on concentration developed in the blood, — for example, salicylates and sulfonamides, — the rate of emptying affects the extent of the therapeutic effect derived from a single dose. Any adjuvant procedure that prevents delay in the emptying of the stomach and obviates variations in the rate of emptying overcomes, at least partially, some of the handicaps of oral therapy. This fact has special importance for drugs which in themselves may delay emptying, as may large doses of acetylsalicylic acid, as has been shown by Schnedorf, Bradley and Ivy.[1]

The study presented here extends the investigations of these authors on the effects of salicylates on the rate of emptying. It further deals with the relation between the rate of emptying and the concentration of drugs developed in the blood and with the influence of acids, alkalies, carbon dioxide and effervescent mixtures on the rate of emptying of the stomach and speed of absorption.

## INFLUENCE OF SALICYLATES ON RATE OF GASTRIC EMPTYING

Schnedorf, Bradley and Ivy have reported delay in emptying of the stomach after oral doses of 1 and 2 gm. of acetylsalicylic acid. To determine whether this delay was due in part to the systemic effects of absorbed salicylate, the emptying time was determined in a series of rats to which the salicylate was administered intravenously. The rate of emptying was evaluated from the percentage retention at two hours of a test meal of 25 per cent solution of dextrose, to the amount of 2.5 gm. of dextrose per kilogram of body weight. Thirty-nine rats were used — 30 as experimental animals and 9 as controls, which received injections of saline instead of the salicylate solution. Thirty minutes after the injection of sodium salicylate or saline solution the test meal was given. Two hours later the animals were anesthetized with sodium amytal, the abdomen was opened, and the stomach was quickly tied off and removed. The amount of unabsorbed dextrose in the stomach contents was determined by the method of Shaffer and Somogyi.[2] The findings are presented in Table 1.

TABLE 1. *Influence of Intravenous Administration of Salicylate on Rate of Emptying of Stomach in Rats.*

| AMOUNT OF SALICYLATE | NO. OF ANIMALS | DEXTROSE RECOVERED FROM STOMACH | |
|---|---|---|---|
| | | EXTREMES | AVERAGE |
| *gm./kg.* | | % | % |
| None | 9 | 0- 5 | 2 |
| 0.05 | 8 | 1- 5 | 2 |
| 0.10 | 8 | 2-39 | 14 |
| 0.25 | 6 | 31-78 | 45 |
| 0.50 | 8 | 55-78 | 66 |

The gastric emptying was not influenced by small doses of salicylate but was markedly delayed by the systemic action of large doses. For doses of 0.05 gm. per kilogram, there was no appreciable delay in emptying time and the retention at two hours averaged only 2 per cent, but with doses of 0.5 gm., 66 per cent of the test meal was still in the stomach at two hours.

The larger doses and correspondingly high concentrations of salicylate in the blood have significance in the therapy of rheumatic fever but none for the use of salicylates for analgesia. To determine the possible effects on gastric emptying of the local action of salicylates on the gastric mucosa in the presence of low concentrations in the blood, as in ordinary analgesic doses, a series of determinations was made on 3 normal human subjects. They were given 0.6 gm. of acetylsalicylic acid and 100 cc. of water and, in control experiments, water but no salicylate. The rate of emptying was determined by fluoroscopic examination at intervals of fifteen minutes, using the test meal and technic developed by Van Lière and Sleeth.[3] The average times were obtained from a number of observations made at intervals of several days. For Subject 1 the average, when water alone was given, was two hours and fifteen minutes and after acetylsalicylic acid, two hours; for Subject 2 the corresponding values were one hour and forty-five minutes and two hours; for Subject 3, they were two hours and one hour and forty-five minutes. It appears that this salicylate has, in ordinary doses given for analgesia, no delaying action from local or systemic effects on the rate of gastric emptying.

*From the Laboratory of Applied Physiology, Yale University.

†Assistant professor of applied physiology, Yale University, and medical director, Yale Plan Clinic.

‡Assistant, Laboratory of Applied Physiology

### Influence of Acids, Alkalies and Effervescent Mixtures on Rate of Gastric Emptying

A comprehensive review of the influence of acids and alkalies on the rate of emptying of the stomach will be found in the writings of Van Lière and Sleeth.[4] In spite of conflicting results the well substantiated findings are as follows. Strong acids inhibit gastric motility, whereas weak acids have an undetermined effect; and moderate amounts of sodium bicarbonate hasten and large amounts slow the emptying time. There is no full agreement among investigators concerning the mechanism involved. Van Lière and Sleeth suggest three hypotheses: an effect on the action of the pylorus; an effect on the secretory activity of the stomach followed by changes in motility and a direct effect on gastric motility. Objections can be raised against all three of these explanations.

In the experiment reported herein 3 normal human subjects were used. The rate of gastric emptying after a test meal, as described above, was determined at intervals of several days. In a series of control determinations made with water administered ten minutes after the test meal, it was found that the rate of emptying for each subject was fairly uniform. The water was replaced on separate occasions by an equal volume of fluid containing 1.5 gm. of tartaric acid, 2.0 gm. of sodium bicarbonate or an effervescent mixture of 1.5 gm. of tartaric acid and 2.0 gm. of sodium bicarbonate. Three determinations were made on each subject for each of the materials administered. The findings are given in Table 2. As seen from this table,

Table 2. *Influence of Tartaric Acid, Sodium Bicarbonate and an Effervescent Mixture on the Rate of Emptying of the Stomach.*

| Subject No. | Gastric Emptying Time | | | |
|---|---|---|---|---|
| | Control | After Sodium Bicarbonate | After Tartaric Acid | After Effervescent Mixture |
| 1 | 2 hr. | 1 hr. | 1 hr., 45 min. | 1 hr., 15 min. |
| | 2 hr. | 1 hr. | 2 hr. | 1 hr. |
| | 2 hr. | 1 hr., 30 min. | 2 hr. | 1 hr. |
| 2 | 1 hr., 30 min. | 1 hr. | 2 hr. | 1 hr. |
| | 1 hr., 30 min. | 1 hr. | 1 hr., 30 min. | 45 min. |
| | 1 hr., 45 min. | 45 min. | 1 hr., 45 min. | 45 min. |
| 3 | 1 hr., 30 min. | 45 min. | 1 hr., 45 min. | 45 min. |
| | 1 hr., 30 min. | 1 hr. | 1 hr., 30 min. | 45 min. |
| | 1 hr., 45 min. | 1 hr., 15 min. | 2 hr. | 45 min. |

the rate of emptying was not appreciably influenced by tartaric acid but was markedly shortened by sodium bicarbonate and by an effervescent mixture of the two substances. These findings will be discussed later.

To avoid continual fluoroscopic procedures and to check the validity of the data obtained by fluoroscopy, the rate of gastric emptying was determined by direct measurement. By means of a Levin tube the stomach contents were withdrawn at intervals and, after the volume had been determined, reinjected into the stomach. Each subject was trained to pass the tube without assistance; after a few days of practice nausea and apprehension, which might affect gastric motility, disappeared. A bouillon test meal was used.

The subjects received their last meal at dinner the day previous to each experiment and no fluid after midnight. At 9 a.m. the tube was passed and the small amount of gastric juice present in the stomach was withdrawn for preliminary determination of the hydrogen-ion concentration. Bouillon was then swallowed and immediately thereafter 100 cc. of the solution under study. The tube was left in place for the duration of the experiment. At intervals of fifteen minutes the stomach contents were withdrawn as completely as possible and measured. A few cubic centimeters was retained for measurement of the reaction, and the remainder was returned to the stomach.

That repeated withdrawal and return had no appreciable influence on the rate of gastric emptying was shown by comparative determinations in which the stomach contents, on one occasion, were removed and returned as described and on another were allowed to remain for an hour before removal. The values obtained are shown in Table 3.

At intervals of several days two additional determinations were made on the two subjects, using 100 cc. of bouillon and 100 cc. of water. The findings

Table 3. *Volume of Stomach Contents with Single and Repeated Withdrawals.*

| Subject No. | Volume of Stomach Contents | | | |
|---|---|---|---|---|
| | 15 min. | 30 min. | 45 min. | 60 min. |
| | cc. | cc. | cc. | cc. |
| 1 | 160 | 140 | 130 | 120 |
| | — | — | — | 110 |
| 2 | 185 | 180 | 140 | 80 |
| | — | — | — | 105 |

are given as the first four values in Table 4. As seen, the residuum at one hour was substantially the same as in the determinations recorded in Table 3.

Again at intervals determinations were made after the subjects were given the following: 100 cc. of bouillon and 100 cc. of effervescent mixture containing sodium bicarbonate (4 gm.) and tartaric acid (3 gm.), but with the mixture boiled to remove all free carbon dioxide and subsequently cooled; 100 cc. of bouillon and 100 cc. of effervescent mixture, not boiled but with active effervescence; and 100 cc. of bouillon and 100 cc. of carbonated water. The findings are given in Table 4. As seen, the effervescent mixture, unboiled, hastened the emptying of the stomach with a residuum averaging 20 cc. at sixty minutes, as compared to 100 cc. for the control experiments. A comparable hastening effect resulted when carbonated water was used instead of the effervescent mixture. A moderate hastening

effect resulted when the effervescent mixture was boiled prior to administration. Under the conditions of these experiments there appeared to be no correlation between the hydrogen-ion concentration of the gastric juice and the extent of gastric emptying.

Tartaric acid was used in this experiment rather than citric acid, which is often employed in effervescent mixtures, to avoid any effects from possible systemic alkalinization due to the oxidation of the citric acid. Tartaric acid in doses of 1.5 gm. has no effect on gastric emptying.

The fact that carbonated water hastens gastric emptying confirms the work of Carnot and Koskowski,[5] Kussmaul,[6] Jaworski[7] and Binet and Lebon.[8] In addition, it casts some light on the possible mechanisms of effervescent mixtures in general. In the experiments reported herein the effect of the effervescent mixture on gastric emptying did not disappear completely after boiling to remove the carbon dioxide from the effervescent mixture. The relative amounts of sodium bicarbonate and tartaric acid in the mixture used were such as to leave an excess of about 1 gm. of bicarbonate after boiling. Such an amount does not seem sufficient to account for the effect observed, which may have been due in part to sodium tartrate. From experiments, to be described later, there is evidence that sodium tartrate hastens gastric emptying. Van Lière and Sleeth[4] have shown that disodium phosphate has this effect.

The greater effect of the unboiled effervescent mixture as compared to the boiled is undoubtedly connected with the liberation of carbon dioxide, which plays a predominant role in shortening gastric emptying following administration of effervescent mixtures. Sodium bicarbonate in normal healthy subjects exerts an action substantially the same as that of the effervescent mixture, and it is our opinion that it acts mainly through the liberation of carbon dioxide by reaction with the hydrochloric acid of the gastric juice.

Shay and Gershon-Cohen[9] investigated the rate of gastric emptying following administration of small and large doses of sodium bicarbonate. In the presence of a normal gastric acidity, a small dose of sodium bicarbonate hastened the emptying of the stomach. In subjects with a hyperchlorhydric response to the test meal, the same dose of sodium bicarbonate caused an even greater hastening in gastric emptying. In those with an achlorhydric response, it had no effect on the rate of emptying. The interpretations made of these findings, in the light of the work presented here, are as follows. In the presence of a normal amount of hydrochloric acid in the gastric juice, the ingestion of moderate amounts of sodium bicarbonate causes liberation of carbon dioxide, with consequent hastening of gastric emptying. In the absence of hydrochloric acid, carbon dioxide cannot be liberated and there is consequently no hastening of gastric emptying. When large amounts of bicarbonate are given only a part reacts with hydrochloric acid in the normal subjects, and it is possible that the large amount of residual alkali counteracts the effects of the carbon dioxide. In hyperchlorhydric subjects, as shown by Shay and Gershon-Cohen, an increased rate of emptying occurs even when large amounts of bicarbonate are given, a result that may possibly be attributed to the greater evolution of carbon dioxide and lesser residual alkali.

If this interpretation of the data of Shay and Gershon-Cohen is correct, the role played by carbon dioxide in hastening gastric emptying seems significant not only when carbonated water is administered but also when sodium bicarbonate and effervescent mixture are given. It should be emphasized that when bicarbonate alone is used in a normal subject, the need is for moderate rather than large doses, and that the effectiveness in hastening gastric motility is, in large part, conditioned on the presence of hydrochloric acid in the stomach.

TABLE 4. *Volume and Hydrogen-Ion Concentration of Stomach Contents after Various Types of Effervescent Mixtures.*

| Subject No. | Procedure | Volume of Stomach Contents | | | | pH of Stomach Contents | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 15 min. | 30 min. | 45 min. | 60 min. | 0 | 15 min. | 30 min. | 45 min. | 60 min. |
| | | cc. | cc. | cc. | cc. | | | | | |
| 1 | Bouillon, 100 cc., and water, 100 cc. .. | 200 | 140 | 125 | 110 | 4.5 | 5.8 | 4.1 | 2.6 | 1.85 |
| | | 160 | 140 | 130 | 110 | 2.5 | 3.9 | 2.2 | 1.6 | 1.3 |
| 2 | Bouillon, 100 cc., and water, 100 cc. .. | 180 | 170 | 140 | 70 | 3.1 | 4.0 | 2.8 | 2.6 | 2.2 |
| | | 220 | 160 | 120 | 110 | 2.5 | 4.5 | 3.6 | 2.0 | 1.5 |
| 1 | Bouillon, 100 cc., and effervescent mixture boiled, 100 cc. ..... | 150 | 150 | 100 | 40 | 2.5 | 4.6 | 3.0 | 2.0 | 1.6 |
| | | 145 | 110 | 60 | 60 | 4.3 | 6.2 | 4.6 | 1.4 | 1.6 |
| 2 | Bouillon, 100 cc., and effervescent mixture boiled, 100 cc. ..... | 160 | 100 | 50 | 45 | — | 6.1 | 5.8 | 4.3 | 1.8 |
| | | 180 | 130 | 90 | 40 | — | 6.8 | 6.6 | 5.0 | 3.8 |
| 1 | Bouillon, 100 cc., and effervescent mixture, 100 cc. ..... | 140 | 40 | 30 | 20 | 2.8 | 5.8 | 2.4 | 1.5 | 1.4 |
| | | 145 | 60 | 30 | 30 | 3.2 | 6.0 | 1.9 | 1.5 | 1.5 |
| 2 | Bouillon, 100 cc., and effervescent mixture, 100 cc. ..... | 85 | 25 | 15 | 0 | — | 5.9 | 3.2 | 1.4 | 1.4 |
| | | 185 | 120 | 65 | 30 | | | | | |
| 1 | Bouillon, 100 cc., and carbonated water, 100 cc. ..... | 175 | 125 | 75 | 30 | 2.6 | 2.8 | 1.8 | 1.8 | 1.8 |
| | | 165 | 50 | 30 | 15 | — | — | — | — | — |

## Influence of Gastric Emptying Time on Absorption of Drugs

The concentration of sulfathiazole in the blood was determined in 2 subjects at intervals after taking 0.25, 1.0 and 3.0 gm. of the drug, with and with-

out an effervescent mixture consisting of sodium bicarbonate and tartaric acid. The findings are shown in Table 5. The use of the effervescent mixture favors a high concentration in the blood in the early phase of absorption, which is especially marked with the small and moderate doses.

Rapid absorption with an earlier rise of the concentration of the drug in the blood is perhaps of less specific therapeutic importance with a drug such as sulfathiazole, with which prolonged maintenance of concentration is desired, than with acetylsalicylic acid used as an analgesic, with rapid action as a desideratum. It should be borne in mind, however, that the more rapid emptying correspondingly limits the possible gastric irritation from the drug.

Similar experiments carried out with acetylsalicylic acid were intended not only to determine the influence of the effervescent mixture on emptying of the stomach but also to clarify the part played by the carbon dioxide liberated and by the salts formed from the effervescent mixture. Acetylsalicylic acid in doses of 0.6 and 1.6 gm. was given to 2 fasting subjects with an effervescent mixture of tartaric acid (3 gm.) and sodium bicarbonate (4 gm.) with sodium citrate (4 gm.), with sodium tartrate (4 gm.) and with carbonated water (150 cc.). The findings are given in Table 6.

The most striking feature is the higher concentration of salicylate in the blood up to two hours for doses of 0.6 gm. and to four hours for doses of 1.6 gm. when given with various adjuvants. The effervescent mixture was the most effective in increasing the concentration. The increase in concentration signifies a definite benefit in rapid therapeutic action.

These experiments appear to indicate that small amounts of markedly alkaline salts hasten the emptying time of the stomach irrespective of the production of carbon dioxide; that carbon dioxide alone hastens gastric emptying; and that in interpreting the action of an effervescent mixture the following factors enter into consideration: the carbon dioxide produced, the weak alkaline salts formed from the reaction inducing the effervescence and the alkalinity that may occur from an excess of bicarbonate.

TABLE 5. *Blood Concentrations of Sulfathiazole following Its Ingestion with and without an Effervescent Mixture.*

| SUBJECT No. | CONDITION | CONCENTRATION OF SULFATHIAZOLE | | | | |
|---|---|---|---|---|---|---|
| | | DOSE gm. | ½ HR. mg./100 cc. | 1 HR. mg./100 cc. | 1½ HR. mg./100 cc. | 2 HR. mg./100 cc. |
| 2 | After breakfast: | | | | | |
| | No effervescent mixture | 0.25 | 0.04 | 0.24 | 0.33 | — |
| | | 0.25 | 0.06 | 0.10 | 0.22 | — |
| | With effervescent mixture | 0.25 | 0.20 | 0.32 | 0.58 | — |
| | | 0.25 | 0.19 | 0.50 | 0.43 | — |
| 1 | No effervescent mixture | 3.0 | 1.88 | — | 4.60 | 4.93 |
| | With effervescent mixture | 3.0 | 1.55 | — | 4.90 | 5.68 |
| 1 | Before breakfast: | | | | | |
| | No effervescent mixture | 0.25 | 0.30 | 0.55 | 0.76 | — |
| | With effervescent mixture | 0.25 | 0.90 | 0.66 | 0.53 | — |
| | No effervescent mixture | 1.0 | 0.31 | — | — | 1.42 |
| | With effervescent mixture | 1.0 | 1.36 | — | — | 1.54 |

TABLE 6. *Blood Concentrations of Salicylic Acid following the Ingestion of Acetylsalicylic Acid with and without Other Substances.*

| SUBJECT No. | CONDITION | DOSE OF DRUG | CONCENTRATION OF SALICYLIC ACID | | | |
|---|---|---|---|---|---|---|
| | | | ½ HR. | 1 HR. | 2 HR. | 4 HR. |
| | | gm. | mg./100 cc. | mg./100 cc. | mg./100 cc. | mg./100 cc. |
| 2 | Drug alone | 0.6 | 0.80 | 1.80 | 3.80 | 2.65 |
| | Drug and effervescent mixture | 0.6 | 4.33 | 4.10 | 3.53 | 2.20 |
| | Drug and sodium citrate (4 gm.) | 0.6 | 4.25 | 4.06 | 3.87 | 2.60 |
| | Drug and sodium tartrate (4 gm.) | 0.6 | 1.40 | 3.00 | 3.35 | 2.74 |
| | Drug and carbonated water | 0.6 | 1.80 | 3.50 | 3.80 | 2.33 |
| 1 | Drug alone | 1.6 | 1.67 | 3.67 | 5.53 | 7.33 |
| | Drug and effervescent mixture | 1.6 | — | 8.93 | 10.20 | 10.30 |
| | Drug and sodium citrate (4 gm.) | 1.6 | 3.00 | 4.06 | 6.00 | 9.20 |
| | Drug and sodium tartrate (4 gm.) | 1.6 | 4.47 | 5.86 | 10.01 | 8.40 |
| | Drug and carbonated water | 1.6 | 2.53 | 3.86 | 8.34 | 9.85 |

## CONCLUSIONS

Attempts at hastening the rate of gastric emptying seem warranted when a quick effect of a drug orally administered is required with minimum irritation of the stomach. Such attempts seem further justified by the possibility that some drugs delay gastric emptying when given in large amounts.

Evaluation of the rate of gastric emptying by means of fluoroscopic examination, gastric intubation and determinations of blood concentrations of test drugs indicates that effervescent mixtures decrease the emptying time of the stomach.

The effect attendant on the administration of an effervescent mixture seems to be due in part to the presence of weak alkaline salts and in part to the production of carbon dioxide.

### References


1. Schnedorf, J. G., Bradley, W. B., and Ivy, A. C. Effect of acetylsalicylic acid upon gastric activity and modifying action of calcium gluconate and sodium bicarbonate. *Am. J. Digest. Dis. & Nutrition* 3:239-244, 1936.
2. Shaffer, P. A., and Somogyi, M. Copper-iodometric reagents for sugar determination. *J. Biol. Chem.* 100:695-713, 1933.
3. Van Liere, E. J., and Sleeth, C. K. Some normal variations in emptying-time of human stomach, using carbohydrate meals. *Am. J. Digest. Dis. & Nutrition* 2:671, 1935.
4. *Idem*: Emptying time of normal human stomach as influenced by acid and alkali with review of literature. *Am. J. Digest. Dis.* 7:118-123, 1940.
5. Carnot, P., and Koskowski, W. Action de l'acide carbonique sur la motricité gastrique et sur le passage pylorique. *Comptes rend. Soc. de biol.* 87:613-616, 1922.
6. Kussmaul, A. Die peristaltische Unruhe des Magens, nebst Bemerkungen über Tiefstand und Erweiterung desselben, das Klatschgeräusch und Galle im Magen. *Sammlung klin. Vorträge* 181: 1637-1674, 1880.
7. Jaworski, W. Vergleichende experimentelle Untersuchungen über das Verhalten des Kissinger und Karlsbader Wassers, sowie des Karlsbader Quellsalzes im menschlichen Magen. *Deutsches Arch. f. Klin. Med.* 35:38-78, 1884.
8. Binet, M. E., and Lebon, H. De l'influence du bicarbonate de soude sur la durée de l' évacuation stomacale. *Clinique, Paris* 7:241-243, 1912.
9. Shay, H., and Gershon-Cohen, J. Experimental studies in gastric physiology in man: study of pyloric control: rôles of acid and alkali. *Surg., Gynec. & Obst.* 58:935-955, 1934.


# MEDICAL PROGRESS

## NEUROLOGY


H. Houston Merritt, M.D.*

NEW YORK CITY


THE significant publications in the field of neurology in 1945 included a number of studies on the physiology of the nervous system, further reports on the use of antibiotics in the infections of the nervous system, including syphilis and tuberculous meningitis, the introduction of a new drug in the treatment of petit-mal epilepsy and articles on various miscellaneous subjects.

### Physiology

Two studies on the physiology of the pyramidal tract have been contributed by Lassek.[1, 2] In the first he correlated the occurrence of the Babinski reflex with the other evidence of damage to the corticospinal tract. The material used in this study comprised 1600 case reports collected from the literature in which the Babinski sign was exhibited. The Babinski reflex was present bilaterally in 85 per cent of the 200 cases that showed various degrees of suppression of the somatic nervous activity, such as that occurring in unconscious states. All degrees of motor activity from normal to complete paralysis were found. The signs and symptoms that accompanied the Babinski sign, in the order of frequency, were somatic motor deficit, hyperactive patellar reflex, absence of abdominal reflex, spasticity, ankle clonus, hypoactive knee jerk, absence of cremasteric reflex, flaccidity and patellar clonus.

In the second study, Lassek attempted to determine the frequency of changes in the axones in the pyramids in patients who had evidence of cerebrovascular lesions during life. Sections of the medulla of 166 such patients were stained by the Davenport method. There was complete destruction of the axones in the pyramids in only 7, and partial damage in 36. No loss of fibers in the pyramids could be demonstrated in 63 cases, although many of these patients had a hemiplegia during life. Lassek concludes that hemiparesis or hemiplegia, caused by chronic cerebral vascular lesions, may occur with little or no destruction of the fibers in the pyramid of the medulla.

Studies in disturbances of the sleep mechanism were made by Davison and Demuth.[3, 4] In 9 patients pathologic sleep was associated with lesions confined to the cortex. Increased intracranial pressure was present in only 4 of these cases, and compression of the hypothalamus was excluded in 7. From their histologic study of the brains of these 9 cases, the authors conclude that some fibers for the cortical control of sleep originate in the cerebral cortex, especially the hippocampal, cingular, frontal and temporal convolutions. In 25 patients with pathologic sleep there was involvement of the corticodiencephalic structures. The hypothalamus was invaded or compressed in 16 cases, and the basal ganglia were involved in 16. The authors state that fibers for the control of sleep, which originate in the cortex, reach the hypothalamus by way of the median forebrain bundle, the fornix and the inferior thalamic peduncle.

The effect on the nerve-action potential of various choline esterase inhibitors was studied by Bullock, Nachmansohn and Rothenberg.[5] They have found that strychnine, eserine and cocaine reversibly depress the action potential of the giant axone of


*Professor of clinical neurology, College of Physicians and Surgeons, Columbia University; chief of Division of Neuropsychiatry, Montefiore Hospital.

the squid. Prostigmine, despite its in vitro action on choline esterase, does not affect the action potential because it is a quartanary ammonium and cannot penetrate a lipidoid membrane. The authors consider their findings to be consistent with the theory that acetylcholine is the depolarizing agent released during the passage of the impulse and that the physiologic role of choline esterase should be the rapid removal of the ester; inhibition of the enzyme should result in enduring depolarization and therefore abolition of conductivity.

The sympathetic dermatomes in the lumbar and sacral regions are outlined by Richter and Woodruff[6] in 75 patients who had sympathectomies in this region. With the electrical skin-resistance method, the area of increased skin resistance followed a definite segmental pattern that corresponded closely to the sensory and vasomotor dermatomes determined by Foerster.

A new method of determining cerebral blood flow in man is described by Kety and Schmidt.[7] The method is based on the principle that the rate at which the cerebral venous blood content of an inert gas (nitrous oxide) approaches the arterial blood content depends on the volume of blood flowing through the brain. Comparison of the results with the use of this method with those obtained by the direct measurement of flow in monkeys showed that the gaseous method was quite accurate.

The effect of the administration of phenobarbital or dilantin on the recovery of motor function following ablation of the fourth and sixth cortical areas in monkeys was studied by Watson and Kennard.[8] Phenobarbital in nonsedative doses retarded the rate of recovery. Dilantin alone had no effect on the rate or recovery of motor function, but dilantin when administered together with doryl inhibited or prevented the enhanced recovery rate that occurs when doryl is given alone.

Richter[9] reports that degenerative changes can be produced in the basal ganglions of monkeys when the animals are chronically poisoned by exposure to carbon disulfide vapor for many months. The pathologic changes consist of extensive necrotic lesions in the globus pallidus and the substantia nigra. The animals present many of the clinical signs often seen in disease of the basal ganglions in man, but the parkinsonian type of tremor has not been observed.

Bender[10] states that although polyopia and monocular diplopia usually are hysterical symptoms, they may occur on an organic basis. He emphasizes the fact that lesions in the occipital lobe or central visual pathways, as well as lesions in the media of the eye, can be followed by polyopia or monocular diplopia.

Curare was used by James and Braden[11] in the treatment of 12 paraplegic patients, injured in war, who suffered with annoying and distracting flexor withdrawal reflexes of the lower extremities. The use of this drug resulted in a decrease in the frequency and severity of the reflexes, with resulting general improvement.

## Infections

A case of tuberculous meningitis in a one-year-old infant treated with streptomycin is reported by Cooke, Dunphy and Blake.[12] The diagnosis was confirmed by cerebrospinal-fluid abnormalities and by guinea-pig inoculation. The streptomycin was administered intramuscularly and intrathecally. The baby had survived for two hundred and thirty-four days since the start of the treatment. The meningitis was apparently entirely cured, but there were residuals indicating severe damage to the nervous system.

Twenty-eight consecutive cases of influenzal meningitis were treated by Smith, Wilson and Hodes.[13] The incidence of influenzal meningitis in infancy follows a curve similar to that of pneumococcal meningitis; that is, most cases occur between the ages of three and nine months. Early diagnosis and intensive therapy, with the use both of sulfonamides and of type-specific antibody, reduced the mortality to 7 per cent, which is comparable to that of meningococcal meningitis. The incidence of serum reactions was high but did not militate against its use.

The neurologic complications of meningococcal meningitis formed the subject of reports by Farmer[14] and by Degen.[15] Focal neurologic signs were present in 26 of the 300 patients reported by Farmer. There were 9 cases with sixth-nerve paralysis, 9 with seventh-nerve paralysis, 5 with eighth-nerve paralysis and 3 with transient focal cerebral complications — convulsions, hemiplegia and aphasia. The sixth-nerve paralysis, which was most often unilateral, developed early in the course of the disease, while the cerebrospinal fluid was purulent, and complete recovery usually occurred within a few weeks. The seventh-nerve paralysis, either unilateral or bilateral, was a late complication, developing five to fourteen days after the onset and at a time when the cerebrospinal fluid was relatively cell free. Recovery from the facial paralysis was usually complete within a few months. Eighth-nerve paralysis occurred more frequently in children than in adults. Both eighth nerves were usually involved, and the hearing loss was permanent. A follow-up study of 986 patients with cerebrospinal meningitis was made by Degen.[15] Sequelae of the meningitis were found in 387 patients, 91 of whom were incapacitated. The sequelae included the following: emotional instability, in 109 patients; headache, in 170; backache, in 46; inability to concentrate and poor memory, in 8; total deafness, in 27; impaired vision, in 22; disturbances of vision, in 7; strabismus, in 9; aphasia, in 2, both patients being over fifty years of age; poor balance, in 20; and dizziness, in 13.

The results of the use of penicillin in the treatment of neurosyphilis are reported from several clinics. Gammon and his associates[16] summarize the changes that occurred in the cerebrospinal fluid of 89 patients treated with 1,200,000 to 4,000,000 units of penicillin. The cell count and protein content of the cerebrospinal fluid was reduced to normal in all but 6 patients. The authors conclude that large doses of penicillin, especially when repeated, give the best results.

O'Leary and his co-workers[17] report their results with the use of penicillin in 100 patients with various types of neurosyphilis. The dosages varied from 1,200,000 to 8,000,000 units, and the routes of administration included the intramuscular, intravenous and intraspinal. The clinical and serologic response in patients with meningeal neurosyphilis was excellent, whereas patients with dementia paralytica were improved only slightly, if at all. The combination of penicillin and fever therapy did not improve the results noted from the fever treatment alone. Good results were obtained in reversing the cerebrospinal fluid abnormalities in patients with asymptomatic neurosyphilis who received 1,200,000 units of penicillin in one week in association with either three spinal drainages or intraspinal treatments with penicillin. The authors conclude that the administration of penicillin by the intravenous, intramuscular or intraspinal route is not capable of controlling the parenchymatous forms of neurosyphilis.

Rose[18] reports the results from the use of penicillin in combination with fever therapy in 140 cases of symptomatic neurosyphilis. The treatment consisted of the intramuscular injection of 3,000,000 units of penicillin combined with a short course of fever therapy, half the amount usually prescribed. The results in 36 patients with reasonably early dementia paralytica were improvement in 24, no change in 11 and worsening in 1. There was improvement in only 1 of the 13 cases of long-standing dementia paralytica. No dramatic change was noted in the course of the patients with tabes dorsalis. The progress of the visual loss was arrested in 5 of 6 cases of optic atrophy. The effect of penicillin on the cerebrospinal-fluid abnormalities compared favorably with that of other forms of antisyphilitic treatment.

The hazards of administration of penicillin and other substances intrathecally is the subject of three articles. Siegal[19] reports the case of a sixty-six-year-old woman with Type 14 pneumococcus meningitis who was treated with sulfadiazine by mouth and with penicillin by the intravenous and intraspinal routes. The patient recovered from the meningitis but developed a flaccid paralysis, complete sensory loss below the level of the tenth thoracic segment and loss of sphincter control. The neurologic residuals were permanent. A case of meningitis with headache, stiff neck and fever following the intrathecal injection of Pantopaque is reported by Tarlov.[20] Biopsy of the meninges confirmed the diagnosis of meningitis. Three cases of spinal arachnoiditis and paralysis following spinal anesthesia are reported by Kennedy, Somberg and Goldberg.[21]

### Convulsive Disorders

Experiments were made by Forster[22] on the effect of acetylcholine on the electrical activity of the cortex of cats. He reported that the electrical discharges thus produced were similar to seizure discharges and were correlated with the muscular components of seizures that followed the application of the acetylcholine to the cortex.

Several new drugs have been tested as anticonvulsants in human beings. Clein[23] reports beneficial effects in grand-mal epilepsy and to a less extent in petit-mal epilepsy by the administration of Hydantal (3-methyl, 5-phenylethyl hydantoin) and phenobarbital. On the basis of 10 cases the author states that Hydantal has all the advantages of previous hydantoin derivatives but is without their toxic effects.

The anticonvulsant activity of sulfoxides and sulfones was tested in animals by Merritt, Putnam and Bywater.[24] Several of the phenyl derivatives of these compounds were found to have anticonvulsive activity in animals. One of these, ethyl phenyl sulfone, was given a clinical trial in patients with epilepsy. It was found that this drug had definite anticonvulsive activity in such patients, but this activity was not sufficiently greater than that of phenobarbital or phenytoin sodium to justify its recommendation for general use.

The use of Tridione (3,5,5–trimethyloxazolidine–2, 4–dione) in the treatment of epilepsy was reported by Thorne,[25] Lennox[26] and DeJong.[27] Thorne administered Tridione to 11 patients with grand-mal seizures and compared the results with that obtained with previous forms of treatment. There was improvement in 3 patients, no change in the frequency of seizures in 6 and death from extraneous causes during treatment in 2. Lennox describes the clinical and electroencephalographic characteristics of petit-mal epilepsy and reports on the effects of administration of Tridione to 50 patients with petit-mal seizures. The drug was effective in controlling the seizures in 28 per cent and reduced their frequency in 52 per cent. In 10 patients who had occasional or frequent grand-mal seizures in addition to the petit-mal attacks, the administration of Tridione did not control the former. The principal side effect of treatment was photophobia, which affected adults and older children more frequently than it did younger children. DeJong administered Tridione in combination with Phenytoin Sodium, phenobarbital and bromides to 6 patients who were subject to minor epileptic seizures classified under the term "psychomotor attacks." Some of these patients also had

grand-mal and petit-mal seizures. DeJong reported that Tridione in dosages of 0.32 gm. three times daily was effective in controlling the psychomotor attacks in cases in which the other anticonvulsive drugs had failed.

### Headache

The observation that distended temporal arteries are sometimes palpable in patients with migraine and that as the attack continues these arteries become more rigid and pipelike and less compressible led Torda and Wolff[28] to try to reproduce these findings in cats. The arteries of the ears of 6 cats were studied after infusion for two hours with a solution containing a vasodilator, acetylcholine being used. Measurements demonstrated thickening of the arterial walls of the infused ears. It was also observed that a vasoconstrictor, ergotamine tartrate, was less effective in constricting arteries with thickened walls than in constricting those with normal walls. It was suggested that with prolonged dilatation during attacks of migraine the cranial arteries may undergo similar changes, thus explaining the rigid pipelike texture of the arteries and the decreased ability of ergotamine tartrate to reduce promptly the intensity of the headache.

Friedman, Brenner and Merritt[29] injected 0.1 mg. of histamine base intravenously in patients subject to recurring attacks of headache and in controls. The headache that usually follows such an injection appeared to be closely dependent on a secondary rise in blood pressure that follows the initial fall, as shown by the absence of such a rise in patients in whom headache failed to develop, the temporary disappearance of amelioration of the headache caused by compression of the carotid artery and the temporary disappearance of the headache following a secondary injection of histamine. Support or the lack of it afforded the walls of the intracranial arteries by the cerebrospinal-fluid pressure seems to play a small part in the production of sueh headaches, as shown by the absence of improvement during jugular compression or, in most cases, during inhalation of an oxygen and carbon dioxide mixture. The essential mechanism of experimentally produced histamine headache seems to be the mechanical stimulation of pain-sensitive structures in or near the walls of intracranial arteries, caused by distention of the relaxed walls by blood driven in under increasing pressure.

### Cerebrovascular Lesions

In a comprehensive review of vascular disease of the nervous system, Aring[30] correlates the various manifestations of cerebrovascular disease with the known facts regarding the physiology of cerebral circulation. He emphasizes the fact that the main factors that control the cerebral circulation are extracerebral. Such occurrences as sudden reduction in systemic blood pressure may be followed by lesions in a brain that has pre-existing pathologic changes in its vessels. Similarly, changes in the permeability of blood vessels in patients with disease of the cerebral vessels may be followed by a cerebrovascular lesion.

Wolf, Goodell and Wolff[31] made a follow-up study of patients with subarachnoid hemorrhage. They found that the mortality rate from the first episode of bleeding was 29 per cent. Fourteen per cent of the patients died from recurrence of the bleeding within two to four weeks, and an additional 5 per cent were dead within one year. On the basis of these findings, the authors recommend that an arteriogram be performed on all patients who come under observation during the first four weeks after a subarachnoid hemorrhage. If an aneurysm is visualized, a craniotomy should be performed and the aneurysm treated surgically. Patients who have had their hemorrhage more than four weeks previously and who have localizing signs of an intracranial mass should receive arteriography and craniotomy if suitable indications exist.

### The Central Nervous System in Various Systemic Diseases

Knutson and Baker[32] studied in detail the tissues in 12 patients who had died of uremia. They state that these cases may manifest symptoms covering the entire field of neuropsychiatry. Most frequently these are convulsions and coma, but in isolated cases unusual syndromes, such as monoplegia, hemiplegia, aphasia and all varieties of mental symptoms, may be present. There were widespread changes in the nervous system involving both the nerve cells and the parenchymal elements. If the disease ran an acute course, the predominant alteration occurred in the cortical neurons. In the chronic cases, the striking changes were parenchymal rather than neuronal, consisting of focal and perivascular demyelination and necrosis, although neuronal changes were also present.

Ferraro, Arieti and English[33] examined the brains of 5 patients with pernicious anemia in whom the manifestations of this disease appeared to have developed in the course of a psychosis. One case of pernicious anemia without psychosis and 1 that developed a psychotic syndrome in the course of an established pernicious anemia were also reported. The psychosis was of the paranoid schizophrenic type, with ideas of persecution and grandeur, and a withdrawal type of behavior. The pathologic picture, which occurred in all cases including the one without neuropsychiatric symptoms, consisted of vascular changes, — mild endarteritis and proliferation, — ischemic cell changes, clumping of glial cells about vessels and the presence of areas of demyelinization that tended to coalesce. In 2 cases the vascular changes typical of Wernicke's encephalopathy were found. These changes were most intense in the regions usually involved in that disease.

Since no mental symptoms were observed in a case that showed the same neuropathologic alterations, the hypothesis is advanced that the organic changes merely precipitate or sensitize one toward a psychosis the type of which is predetermined by psychologic or constitutional mechanisms.

Two cases of disseminated lupus erythematosus with neuropsychiatric symptoms are described by Daly.[34] These symptoms included toxic delirium, frank psychosis, coma and convulsions. Characteristically, neurologic examination showed scattered motor, reflex and sensory changes that shifted rapidly on repeated examination. Pathologically, the essential damage to the brain consisted of extensive vascular changes similar to those found elsewhere in the body, with a diffuse type of nonspecific encephalitis.

Yannet and Lieberman[35] found the incidence of incompatible mother-child Rh blood typings to be significantly higher in a group of undifferentiated mental defectives than in a control group. This suggests that the cerebral abnormality of some of these undifferentiated defectives is probably related to maternal Rh isoimmunization during pregnancy. Of the 19 cases in the undifferentiated group in which this etiologic possibility existed, 6 cases were found in which either definite or presumptive evidence of maternal isoimmunization was present. The neonatal history in all 6 of these cases was considered compatible with the diagnosis of erythroblastosis fetalis. These children showed disorders of muscle tone, choreoathetosis and cerebellar dysfunction.

Two cases of acute idiopathic porphyria are reported by Denny-Brown and Sciarra.[36] In the first case, a brief delirium with tremor, associated with passage of burgundy-colored urine, was followed by recovery. In the second, the more usual abdominal cramps, with delirium, convulsions, severe motor paralysis and passage of burgundy-colored urine, occurred in two attacks separated by an interval of two years. The patient died during the second attack, and pathological examination revealed lesions of an ischemic nature in the peripheral nerves. The possibility of the presence of some locally acting vasoconstrictor substance is discussed in relation to the pathogenesis of the visceral disorders of porphyria.

Hoeffer, Guttman and Sands[37] report 27 cases of verified adenoma of the islet cells of the pancreas with symptoms of hyperinsulinism that were carefully studied from the psychiatric, neurologic and laboratory points of view. A variety of neuropsychiatric manifestations was found in all patients, usually clearly associated with the fasting state, with the patients usually aware of this relation, some having increased their food intake to the point of becoming obese in an effort to forestall attacks. The clinical data fell into four groups. The most frequent autonomic visceral symptoms, occurring in 22 patients, were lightheadedness and sweating, headache and less often abdominal pain, nausea, vomiting, pallor, ravenous hunger and coldness. Somatic neurologic abnormalities were observed in 25 patients. Sixteen had motor symptoms, usually consisting of generalized weakness, tremor and incoordination and less often hemiplegia, — 1 patient had a residual hemiparesis, — diminished or absent reflexes and bilateral Babinski signs. The most frequent sensory symptoms were paresthesias, occurring in 15 patients. Fifteen patients had disturbances of vision or of the extraocular motor system, usually in the form of diplopia, blurring of vision or nystagmus. Five patients had transitory aphasia. Psychomotor symptoms occurred in practically all patients. Most frequently seen were confusional states, dullness and noisy behavior, and less frequently there were inability to concentrate and irritability. Phenomena suggestive of fragmentary or full-blown seizures were noted in 22 patients. Deep coma was seen in 15 patients. Nine showed purposeless random movements, thought by some observers to resemble extrapyramidal dyskinesias. Five patients had fainting spells, 5 had actual grand-mal attacks observed on the wards, and 1 patient had sensory Jacksonian episodes without loss of consciousness. Two patients had staring spells suggestive of petit-mal attacks.

## References


1. Lassek, A. M. Human pyramidal tract. XI. Correlation of Babinski sign and pyramidal syndrome. *Arch. Neurol. & Psychiat.* 53: 375-377, 1945.
2. *Idem.* Human pyramidal tract. XIII. Study of pyramids in cases of acute and chronic vascular lesions of brain. *Arch. Neurol. & Psychiat.* 54:339-343, 1945.
3. Davison, C., and Demuth, E. L. Disturbances in sleep mechanism: clinicopathologic study. I. Lesions at cortical level. *Arch. Neurol. & Psychiat.* 53:399-406, 1945.
4. *Idem.* Disturbances in sleep mechanism: clinicopathologic study. II. Lesions at corticodiencephalic level. *Arch. Neurol. & Psychiat.* 54: 241-245, 1945.
5. Bullock, T. H., Nachmansohn, D., and Rothenberg, M. A. Effects of inhibitors of choline esterase on nerve action potential. *J. Neurophysiol.* 9:9-22, 1946.
6. Richter, C. P., and Woodruff, B. G. Lumbar sympathetic dermatomes in man determined by electrical skin resistance method. *J. Neurophysiol.* 8:323-338, 1945.
7. Kety, S. S., and Schmidt, C. Determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am. J. Physiol.* 143:53-66, 1945.
8. Watson, C. W., and Kennard, M. A. Effect of anticonvulsant drugs on recovery of function following cerebral cortical lesions. *J. Neurophysiol.* 8:221-231, 1945.
9. Richter, R. Degeneration of basal ganglia in monkeys from chronic carbon disulfide poisoning. *J. Neuropath. & Exper. Neurol.* 4: 324-353, 1945.
10. Bender, M. B. Polyopia and monocular diplopia of cerebral origin. *Arch. Neurol. & Psychiat.* 54:323-338, 1945.
11. James, D. F., and Braden, S. Use of curare in treatment of spastic paralysis. *J. Neurosurg.* 3:74-80, 1946.
12. Cooke, R. E., Dunphy, D. L., and Blake, F. G. Streptomycin in tuberculous meningitis: report of its use in one-year-old infant. *Yale J. Biol. & Med.* 18:221-226, 1946.
13. Smith, M. H. D., Wilson, P. E., and Hodes, H. L. Treatment of influenzal meningitis. *J. A. M. A.* 130:331-335, 1946.
14. Farmer, T. W. Neurologic complications during meningococcic meningitis treated with sulfonamide drugs. *Arch. Int. Med.* 76: 201-209, 1945.
15. Degen, J. A., Jr. Sequelae of cerebrospinal meningitis: follow-up study of 986 cases. *Brit. M. J.* 2:243-247, 1945.
16. Gammon, G. D., et al. Penicillin in neurosyphilis: effect on blood and spinal fluid. *J. A. M. A.* 128:653, 1945.
17. O'Leary, P. A., Brunsting, L. A., and Ockuly, O. Penicillin in treatment of neurosyphilis. *J. A. M. A.* 130:698-700, 1946.
18. Rose, A. S. Penicillin treatment of neurosyphilis. *Conn. M. J.* 9: 522-525, 1945.
19. Siegal, S. Transverse myelopathy following recovery from pneumococcic meningitis treated with penicillin intrathecally: report of case, with note on current methods of therapy. *J. A. M. A.* 129: 547-550, 1945.
20. Tarlov, I. M. Pantopaque meningitis disclosed at operation. *J. A. M. A.* 129:1014-1016, 1945.

21. Kennedy, F., Somberg, H. M., and Goldberg, B. R. Arachnoiditis and paralysis following spinal anesthesia. *J. A. M. A.* **129**:664-667, 1945.
22. Forster, F. M. Action of acetylcholine on motor cortex: correlation of effects of acetylcholine and epilepsy. *Arch. Neurol. & Psychiat.* **54**:391-394, 1945.
23. Clein, N. W. New anticonvulsant in treatment of epilepsy: 3-methyl 5, 5-phenylaethylhydantoin (hydantal): preliminary report. *Northwest Med.* **44**:210-212, 1945.
24. Merritt, H. H., Putnam, T. J., and Bywater, W. G. Anticonvulsant activity of sulfoxides and sulfones. *Arch. Neurol. & Psychiat.* **54**: 319-322, 1945.
25. Thorne, F. C. Anticonvulsant action of tridione: preliminary report. *Psychiat. Quart.* **19**:686-691, 1945.
26. Lennox, W. G. Petit mal epilepsies: their treatment with tridione. *J. A. M. A.* **129**:1069-1074, 1945.
27. DeJong, R. N. Effect of tridione in control of psychomotor attacks. *J. A. M. A.* **130**:565-567, 1946.
28. Torda, C., and Wolff, H. G. Experimental studies on headache: transient thickening of walls of cranial arteries in relation to certain phenomena of migraine headache and action of ergotamine tartrate on thickened vessels. *Arch. Neurol. & Psychiat.* **53**:329-332, 1945.
29. Friedman, A. P., Brenner, C., and Merritt, H. H. Experimental evidence of physiologic mechanism of certain types of headache. *Arch. Neurol. & Psychiat.* **54**:385-388, 1945.
30. Aring, C. D. Vascular diseases of nervous system. *Brain* **68**:28-55, 1945.
31. Wolf, G. A., Goodell, H., and Wolff, H. G. Prognosis of subarachnoid hemorrhage: and its relation to long term management. *J. A. M. A.* **129**:715-718, 1945.
32. Knutson, J., and Baker, A. B. Central nervous system in uremia: clinicopathologic study. *Arch. Neurol. & Psychiat.* **54**:130-140, 1945.
33. Ferraro, A., Arieti, S., and English, W. H. Cerebral changes in course of pernicious anemia and their relationship to psychic symptoms. *J. Neuropath. & Exper. Neurol.* **4**:217-239, 1945.
34. Daly, D. Central nervous system in acute disseminated lupus erythematosus. *J. Nerv. & Ment. Dis.* **102**:461-465, 1945.
35. Yannet, H., and Lieberman, R. Central nervous system complications associated with kernicterus. *J. A. M. A.* **130**:335-340, 1946.
36. Denny-Brown, D., and Sciarra, D. Changes in nervous system in acute porphyria. *Brain* **68**:1-16, 1945.
37. Hoeffer, P. F. A., Guttman, S. A., and Sands, I. J. Convulsive states and coma in cases of islet cell adenoma of pancreas. *Am. J. Psychiat.* **102**:486-495, 1946.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 32291

#### PRESENTATION OF CASE

A forty-eight-year-old man entered the hospital because of painless jaundice.

For three weeks before admission the patient was easily fatigued. His weight dropped from 170 to 150 pounds. Three weeks before admission his wife noticed that his skin was yellow, and a physician pointed out that the urine was dark and the stools light. In the last week before admission there was generalized itching of the skin. There had been anorexia for the previous two days, but no nausea, abdominal pain or tenderness, or fever. There had been no previous episodes of jaundice and no history of excessive alcohol consumption.

On physical examination the skin, scleras and mucous membranes were deeply jaundiced. The heart sounds and breath sounds were faint, and the lung fields were hyper-resonant. The neck veins were full in the upright position. The liver edge extended 2 cm. below the costal margin and was not tender. The left border of the prostate felt hard and slightly irregular, but there was no enlargement. There was no edema or ascites. The tongue was normal. The spleen was not palpable.

The temperature was 99.8°F., the pulse 70, and the respirations 20. The blood pressure was 96 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,100,000 and 11.8 gm. of hemoglobin. The white-cell count was 8000, with 60 per cent neutrophils. The urine had a specific gravity of 1.012 and gave a ++++ reaction for bile. The stools, which varied from clay colored to brown, were guaiac negative on five of eight examinations and positive on the others. A chest film and a gastrointestinal series were negative. The serum bilirubin was 29.9 mg. per 100 cc. direct, and 38.0 mg. indirect; the total protein was 6.9 gm., the albumin 4.2 gm. and the globulin 2.7 gm. per 100 cc. A cephalin flocculation test was ± at twenty-four hours and ++ at forty-eight hours. The total cholesterol was 255 mg. per 100 cc., with 65 per cent cholesterol esters, the phosphorus 2.8 mg., the nonprotein nitrogen 19 mg. per 100 cc., and the alkaline phosphatase 9.2 Bodansky units. The prothrombin clotting time was 20 seconds (normal, 19 seconds). Duodenal drainage yielded colorless fluid with a pH of 7.4; the sediment contained innumerable white cells that were not bile stained, and no cholesterol crystals or calcium bilirubinate pigment was seen.

In the hospital the temperature ranged from 99.8°F. to normal and subnormal.

An operation was performed on the fifth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. ALFRED KRANES: This case is fairly typical of a group of cases that to my mind are clinically undiagnosable, usually for quite a long period. The group comprises cases of deep painless jaundice of relatively short duration in which the laboratory findings, physical examination, x-ray films and history are essentially negative. The diagnosis is ultimately made in one of two ways: either by the passage of time, during which the patient gets well, or at operation as in the case under discussion. I am not at all sure that, confronted with a similar problem, I should have had the patient operated on quite so soon. I think that less harm is done by a delay of several weeks than by operating needlessly on a patient with hepatitis. For the problem here is whether this patient had acute hepatitis or obstructive jaundice. Since the advent of vitamin K therapy it is no longer dangerous to postpone surgery for a week or two while the patient is under intensive medical care. On the other hand, it is inadvisable to operate on a patient with acute hepatitis.

The real decision is whether the patient had obstructive jaundice. If he did, the nature of the obstruction is nothing more than a guess. On the whole the evidence favors an obstructive type of jaundice, but I do not believe that one can be certain of that from the evidence at hand.

Reviewing the history and physical examination, one would like to know what this patient's occupation was, to make certain that there were no occupational hazards, so far as liver intoxication is concerned, and whether he was taking any drugs. Presumably neither one of these factors was important in this case; otherwise, it would probably have been mentioned. I am somewhat puzzled about the history. The fact that the patient's weight went from 170 to 150 pounds without any obvious reason is quite puzzling. It is stated that anorexia did not develop until a few days before admission, and yet during the period before admission the patient lost 20 pounds. I am inclined to believe that the disorder of appetite must have been present for a considerable time. One would like to know whether the patient consulted a physician simply because his wife had noticed that the skin was yellow or whether he had symptoms at that time. The statement is made at the beginning that the stools were light colored, and it would help considerably to know whether they remained light colored during that three-week period at home. Later, when he entered the hospital, the stools were not consistently clay colored, so that if any obstruction were present one can assume that it was not constant, since bile pigment was getting through.

The physical examination adds nothing to the picture. The only finding that may need comment is the hard and irregular prostate. It is difficult to believe that that casts any light on the problem, even assuming that the prostate was carcinomatous. I cannot conceive that such a degree of jaundice was caused by metastatic carcinoma of the liver, which rarely produces jaundice, except in the terminal stages, when almost the entire liver is replaced by metastatic tumor tissue.

So far as the laboratory work is concerned, the most important finding was in the stools, which varied from clay colored to brown, indicating that bile was getting through occasionally. The fact that a duodenal drainage done later yielded a colorless fluid simply means that no bile was getting through at that particular time; one must not assume that the obstruction was complete.

I do not know just how to interpret the guaiac-negative and guaiac-positive stools. One naturally assumes that a guaiac-positive stool in the presence of weight loss and intense jaundice signifies some neoplastic lesion in the duodenal region. That is not necessarily true: people with jaundice have guaiac-positive stools. Deeply jaundiced people have a hemorrhagic tendency, although the prothrombin time in this case was normal. One would like to know how positive the stools were, whether + or ++++. The rest of the laboratory findings except for the van den Bergh reaction are not helpful. One or two straws in the wind point toward an obstructive lesion — the elevated cholesterol and cholesterol ester ratio, and the elevated alkaline phosphatase. Neither one is conclusive, to be sure, but both suggest an obstruction of the biliary tract.

DR. TRACY B. MALLORY: The guaiac reactions of the stools were + and ++.

DR. KRANES: In that case we cannot attach too much significance to the stools. I am still somewhat puzzled and find it difficult to decide whether the jaundice was or was not obstructive. On the whole the evidence is slightly in favor of an obstructive lesion, but I should like to point out that everything recorded could well be found in a case of acute hepatitis. Certainly many patients with severe cases of hepatitis have persistently clay-colored stools. If this patient were twenty-eight years of age instead of forty-eight there would be little doubt about the advisability of waiting to find out what course the disease might take. At the former age acute hepatitis is more frequent than obstructive lesions of the biliary tract. But the patient was forty-eight, and at that age acute hepatitis is less frequent. It does occur, however, and must be kept in mind. At the age of forty-eight, with a history like this, the chances are in favor of an obstructive lesion of the common duct, which is what I believe this patient had, although one cannot be sure.

Having assumed that it was an obstructive lesion, all one can do is guess its nature. There are two main possibilities: obstruction by a stone and neoplastic obstruction of the common duct. We have all encountered cases of gallstone obstruction that were painless, but I should expect some sort of abdominal distress. A complete and totally painless jaundice with stones seems unusual and is unlikely in this case. The betting is somewhat in favor of a neoplastic lesion, probably a carcinoma of the common bile duct or of the ampulla, or a carcinoma of the head of the pancreas. Certainly the weight loss, the clay-colored stools, the elevated cholesterol and cholesterol esters and the positive guaiac tests on the stool make such a diagnosis at this age more attractive than any other diagnosis. Although I still do not know what this man had, the most probable lesion is a carcinoma of the ampulla or bile duct, an obstructive lesion, but it would not surprise me if it turned out to be acute hepatitis.

DR. ROBERT S. PALMER: Would Dr. Kranes consider doing a liver punch biopsy?

DR. KRANES: I think that a peritoneoscopy and biopsy of the liver before actual surgery would be a logical procedure rather than waiting too long.

DR. MALLORY: A peritoneoscopy was done.

DR. EDWARD B. BENEDICT: No lesion was grossly visible in the liver, but we took a biopsy that gave us the answer.

DR. MALLORY: Unfortunately the biopsy did not exactly give us the answer.

DR. BENEDICT: At least it gave us a pathological report.

### CLINICAL DIAGNOSIS

Carcinoma of head of pancreas?
Carcinoma of ampulla of Vater?
Infectious hepatitis?

### DR. KRANES'S DIAGNOSIS

Carcinoma of common duct?
Acute hepatitis?

### ANATOMICAL DIAGNOSIS

**Infectious hepatitis.**

### PATHOLOGICAL DISCUSSION

DR. MALLORY: The biopsy was done during a period when I was absent from the city. The clinicians were impatient for an immediate diagnosis and were content with an oral report from one of the junior men, who believed the lesion to be consistent with obstructive jaundice. Without further delay an exploratory laparotomy was done. No evidence of obstruction was found, and another biopsy of the liver was done. Following operation the patient's jaundice temporarily increased, after which he began a slow but apparently complete recovery and left the hospital entirely well.

When I returned and was shown the first biopsy specimen I considered it reasonably typical of infectious hepatitis. It showed periportal inflammatory infiltration of mononuclear cells, foci of intralobular inflammation and acidophilic necrosis of individual liver cells. In the second specimen the process had cleared to a considerable degree, and the diagnosis was more difficult. I have had the advantage of seeing a large number of biopsies of cases of epidemic hepatitis during my experience in the Army. Before this experience I have no confidence that I should have recognized the lesion. Most pathologists expect to find extensive central necrosis, such as is seen at autopsy in fatal cases. In nonfatal cases this necrosis is rarely found.

DR. BENEDICT: How do you explain the marked weight loss and absence of fever?

DR. MALLORY: Fever is a variable symptom and is most frequently seen in the prodromal period before jaundice. I cannot explain the weight loss.

DR. KRANES: I should like to ask the surgical point of view on how long to wait when it is difficult to decide. What harm comes to these patients under careful observation?

DR. FIORINDO A. SIMEONE: The longer one allows the obstruction to continue, the greater the chance of irreparable harm to the liver cells and the more difficult it is to correct a disturbance such as the prothrombin formation.

DR. CLAUDE E. WELCH: There is an additional consideration: if this had been a carcinoma of the ampulla, it might have passed the curable stage during the period of observation.

DR. KRANES: How long would that be? It is difficult to believe, since the patient had been jaundiced for three weeks, that two weeks' observation would make such a difference.

DR. WELCH: I should hesitate to wait longer than two weeks. It is a difficult decision to make.

---

## CASE 32292

### PRESENTATION OF CASE

A twenty-five-year-old man, a window decorator, entered the hospital because of dizziness, double vision, headache, nausea and vomiting.

The patient had always been in good health except for occasional "sinus trouble," which was never severe enough to cause him to consult a physician. Five years before admission the patient was discharged from the Army because of bilateral otosclerosis and deafness. Six weeks before entry he noted the sudden onset of dizziness while decorating a window. Things seemed to dance up and down in front of his eyes. A physician found "low blood pressure." Five weeks before entry, the patient became aware of diplopia when looking to the extreme right or left. A week later he rapidly developed a severe dull, nonthrobbing, frontal headache. These symptoms persisted, and three weeks before entry he became nauseated and vomited several times. Associated with the dizziness was some stumbling and clumsiness of gait. A week before entry he became drowsy and had difficulty in remembering where he put things. He experienced some chilly sensations but never had a frank chill. Vision was blurred. Four days before entry the nausea had progressed to such an extent that he ate nothing and drank very little. Two days later he was forced to stop work and slept most of the time. He was finally brought by ambulance to the Emergency Ward.

Physical examination revealed a drowsy, slightly obese young man who yawned frequently. Speech was slow but distinct, and he gave an adequate history. The cranium, chest, heart and abdomen were normal. On confrontation the visual fields were normal. The pupils were equal (4 mm.) and did not react to light but did react to near vision, although there was absence of convergence. No spontaneous nystagmus was present, but there was nystagmus retractorius of the left eye. Conjugate upward gaze was paralyzed, and downward gaze was weak; lateral conjugate gaze was present to a limited degree. For days all eye movements became progressively weaker and eventually paralyzed. The nystagmus retractorius disappeared, but there was vertical nystagmus on attempted downward gaze. Attempted lateral gaze result-

ed in a slight convergent movement of the left eye. There was no opticokinetic nystagmus.

The fundi were normal on admission, but in a week, papilledema (1 or 2 diopters) was present, in addition to a small flame-shaped retinal hemorrhage on the left side that was followed in a few days by a similar hemorrhage on the right. Hearing was markedly impaired bilaterally. The neck was quite stiff. The fifth, seventh, tenth, eleventh and twelfth nerves were normal. There was some unsteadiness in performing the finger-to-nose test on the right, and the Kernig test was positive. The arm and knee jerks were difficult to elicit and were bilaterally equal. The ankle jerks were ++ and equal. There was a flexor-plantar reflex bilaterally.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 5,360,000, with 110 per cent hemoglobin, and a white-cell count of 9040, with 76 per cent neutrophils. The nonprotein nitrogen, chlorides, carbon dioxide and fasting blood sugar were normal. Repeated blood cultures were negative. The blood Hinton test was negative. Lumbar puncture yielded an initial pressure equivalent to 215 mm. of water and a final pressure equivalent to 130 mm. The spinal fluid was questionably xanthochromic and contained 6 red cells, 45 lymphocytes and 6 polymorphonuclears per cubic millimeter. The protein was 98 mg., the sugar 11 mg. and the chlorides 680 mg. per 100 cc. The urine had a specific gravity of 1.022 and was normal except for a ++ test for acetone. There was no albumin or sugar. Smear and culture of a pellicle formed on standing were negative for tubercle bacilli. A guinea pig was inoculated. A tryptophane test on the spinal fluid was positive.

A tuberculin skin test was negative in a dilution of 1:1000. X-ray films of the chest and skull were negative. The pineal body was not visualized.

The patient continued to be drowsy but could be aroused. On the third hospital day the temperature suddenly rose to 105°F., and he became stuporous and incontinent. No reflexes could be obtained. The plantar reflexes were flexor bilaterally. He was given alcohol sponges and penicillin. At no time did he receive sulfonamides. The temperature continued to climb, reaching a peak of 107°F. on the fourth hospital day. On the sixth day it was down to 99°F., but rose again to 104° in the evening and gradually dropped to 99°, running a moderate spiking course. The state of consciousness approximately paralleled the temperature, but the patient never regained full consciousness. On repeated lumbar punctures the spinal-fluid pressure was equivalent to 230 to 300 mm. of water. The fluid was xanthochromic, with 20 to 25 white cells per cubic millimeter, of which a few (1 to 6) were polymorphonuclears. The total protein remained elevated (56 to 98 mg. per 100 cc.). The sugar rose to 65 and 89 mg. per 100 cc. (punctures performed following infusions of 5 per cent dextrose in saline), and the chlorides rose to 827 milliequiv. per liter. The gold-sol curve was 0001121100. Dynamics, performed on the fourth lumbar puncture, were normal.

On the twelfth hospital day a red petechial eruption, which blanched on pressure, appeared over the back, dependent regions of the shoulders and upper arms, gradually spreading over the entire body and assuming a maculopapular character. On the following day the nonprotein nitrogen was 205 mg. per 100 cc. The patient was totally incontinent, passing many diarrheal stools that were negative for pus, parasites and occult blood. On the fifteenth hospital day the nonprotein nitrogen had risen to 260 mg. per 100 cc. The carbon dioxide was 12.1 milliequiv. and the chlorides 104 milliequiv. per liter. An inlying catheter was placed, and although oliguria had been suspected the measured output rose to approximately the intake. The specific gravity was 1.010 on repeated examinations, and a ++ test for albumin was found. Abundant colon bacilli were grown in urine culture. Repeated chemical determinations showed continued high nonprotein nitrogen, reaching 290 mg. per 100 cc. on the twentieth hospital day. The carbon dioxide content, however, gradually rose to 20.9 milliequiv. per liter. On the sixteenth hospital day an x-ray film of the chest revealed a definite increase in density in the left-lower-lung field. Moist rales became audible at the left base, and the patient developed chills and rapid, shallow respiration. His condition grew rapidly worse, and he died on the twenty-fourth hospital day.

## Differential Diagnosis

Dr. Mandel Cohen: This man was apparently well until the onset of the present illness and over a period of six weeks developed, successively and rapidly, dizziness, slight diplopia, nausea, vomiting, stumbling and drowsiness. He was taken to the hospital, where it was found that he had some signs indicating that the midbrain and the cerebellum were involved. A few cells were found in the spinal fluid, and there was fever. The question no doubt came up whether the disorder was infection or neoplasm. He became worse and, after being in the hospital for twelve days, developed nitrogen retention and a rash. Nitrogen retention progressed, and death followed.

From these data it is not possible to determine exactly the nature of this disorder. There were, however, signs and symptoms that point fairly definitely to the location and that give a lead regarding the possible causes of the lesion. To begin with, the symptoms of dizziness, diplopia, nausea, vomiting, stumbling and drowsiness could be related to disease involving the cerebellum or cerebellar connections. The neurologic examination showed

predominantly difficulties with eye movements that were not paralysis of isolated nerves but concerned conjugate movement, upward movement, downward movement and lateral movement; in addition, the pupils measured 4 mm. and did not react to light, but did react during accommodation. Convergence of the eyes was absent. All that taken together means that the midbrain was involved. Was it involved by a mass in the midbrain, or was it involved by something pressing on the midbrain? I cannot tell the difference. Incidentally the patient had nystagmus retractorius. After a certain amount of investigation and aid from Dr. Cogan, I discovered the meaning of this term. When co-ordination of eye movements is poor all the muscles may move together. An attempted eye movement results in eye retraction; this is supposed to be due to distribution of connections of the nuclei of the third nerve. All these eye signs point definitely to disorder affecting the midbrain. One might ask why we did not think that the nerves individually were involved. The patient did not have obvious strabismus, it was not possible to demonstrate isolated paralysis of nerves, and the eyes followed objects. Midbrain localization was therefore indicated. It is probable that the lesion or lesions were in the neighborhood of the midbrain and the anterior part of the cerebellum.

The next question to decide is the nature of the disorder. Because of the progressive course, this disorder probably was not a thrombosis of the blood vessel or vascular disease; because of the evidence of increased intracranial pressure and the lack of other typical signs, it was probably not any of the so-called "degenerative diseases," such as acute encephalomyelitis and multiple sclerosis. That leaves the problem of what could cause increased intracranial pressure and develop rapidly within about six weeks, with death following soon thereafter. It seems to me that one cannot tell absolutely whether this was a tumor or an infectious disorder. The course of the illness, which was rather brief for that of tumor, suggests some infectious disorder. Neoplasm involving the area of the midbrain, however, often runs a rapid course. In Dandy's[1] series some tumors of the third ventricle ran half a year's course between the first symptom and operation. The short course is therefore not diagnostic, except that it is somewhat short for a tumor.

In considering infectious disorder of the brain, one must include an infectious mass — that is, abscess or tuberculoma. One would then like to have some idea of what such a mass is secondary to, because by and large, if a patient has brain abscess or tuberculoma, there is some evidence of primary infectious disease. There was no evidence of tuberculosis in the lungs or elsewhere or of a focus of infection suggesting a brain abscess. Five years before admission the patient was discharged from the Army because of bilateral otosclerosis and deafness. I wonder whether he had bilateral otitis media all the time, but I assume that the ears were examined in this hospital and were normal. Apparently this patient's "sinus trouble" was never severe enough for him to consult a physician. That type of history is of no help in an attempt to find the focus of infection for brain abscess. Usually clear-cut evidence of otitis media, sinusitis or lung disease is found, but this patient did not have such evidence. That is a serious drawback to the diagnosis of infection, such as abscess.

Does the fever help in the differential diagnosis? By and large, it is safe to assume that if the patient had fever he had infection. One serious exception, however, is when a patient has disease around the midbrain and hypothalamus, which I suppose is exactly where the disease occurred in this patient. There are well authenticated cases of continuous fever from lesions in that region. In general, most diagnoses of neurogenic fever and probably all so-called "psychogenic fever" lead to the wrong answer. Consequently even fever does not help in the decision between tumor and infection.

Does the spinal fluid help in the differential diagnosis? The few cells make one think not of obvious meningitis but of a mass like abscess or tuberculoma that is irritating but does not actually infect the ventricular and subarachnoid spaces. Tumors, particularly those involving the third ventricle or other ventricles, also give a few cells and even a few polymorphonuclears. What about the spinal-fluid sugar? In general, a low spinal-fluid sugar means the active presence of bacteria, tubercle bacilli or yeast. The first sugar determination was quite low (11 mg. per 100 cc.), and subsequent tests were within normal limits. One possibility is that the first sugar determination was wrong — that the fluid stood for a day or two before analysis.

Dr. James Meath: The first sugar determination was done on the day following lumbar puncture.

Dr. Cohen: The lumbar puncture was done, and the fluid stood over night and was analyzed later. Falsely low sugars can be obtained under such circumstances. That is quite possible in this case because the cells were not high enough to go with such a low sugar. The blood sugar level affects the spinal-fluid sugar: with a high blood sugar after a clysis or intravenous injection the spinal-fluid sugar may be falsely high. In bacterial infection it is also possible for patients being treated with penicillin to have bacteria in the spinal fluid, the sugar remaining high in the presence of penicillin. Apparently under these conditions bacteria are not able to use sugar. All one can say is that the patient had one quite low sugar and two normal ones. In tuberculous meningitis, if the sugar is once low, it is apt to remain low. The cultures, I gather, were all normal. Were cultures taken of the spinal fluid when the patient was not getting penicillin?

Dr. Meath: Yes.

DR. COHEN: Final conclusions cannot be drawn from a good part of the data. One must say that the course could be tumor or infection, and the spinal fluid could go with either. There was no good source for infection.

We are left with the possibility of a mass that was in the cerebellum, pressing on the midbrain or, less likely, in the midbrain itself and was either neoplastic or infectious in origin. If infectious, the mass was probably tuberculoma or something of that sort rather than an abscess.

The neurologic disorder progressed, and on the twelfth day a petechial eruption of a maculopapular character developed; from that point on nitrogen retention was noted. The nonprotein nitrogen rose steadily, and there were acidosis and diarrhea. All we are told about renal studies is that cultures gave abundant colon bacilli. The patient presumably did not have pus in the urine. Is that right?

DR. TRACY B. MALLORY: When he first came in he had a specific gravity running from 1.020 to 1.030, with no albumin and only one or two white cells per high-power field on smear. Terminally, after he had an inlying catheter for many days, there was pus in the urine.

DR. COHEN: The patient then developed what seemed to be pneumonia and died. How can one relate this development of uremia with the intracranial disease? One can speculate about various syndromes associated with brain and renal disease, but none of them seem clinically applicable in this case. Could there have been hypertension or vascular disease of a malignant type, which led to brain lesions and then to renal failure? This case does not give the picture of that syndrome, either by course or by signs. Another possibility is a renal tumor that metastasized to the brain and later showed itself as renal disease; again, there is no evidence whatsoever. Other conditions such as periarteritis nodosa which involve the brain and kidney, can be mentioned, but there is no evidence.

Were any drugs besides penicillin given?

DR. MALLORY: No.

DR. COHEN: Does penicillin, like the sulfonamides, cause uremia? The only evidence is that nitrogen retention occasionally occurs during the administration of penicillin, but for all practical purposes a renal complication is not attributable to penicillin.

Could this patient have had a bacterial infection, septicemia, brain infection and, terminally, renal infection? Again, there is no evidence. I gather that there was no retrograde pyelogram or anything like that, which might have helped somewhat.

Could tuberculosis of the kidney have been associated with the alleged tuberculoma of the brain? That is not likely; the uremia would not be consistent with the brain disease. Perhaps cystitis and pyelonephritis developed terminally. That is not a satisfactory explanation, but I do not see any other, in the absence of drugs such as sulfanilamide.

In conclusion, this man had a disease that came on fairly rapidly and seemed to involve the region of the cerebellum and the midbrain, causing increased intracranial pressure, fever and cells in the spinal fluid. Further information in such a situation could be obtained from injections of air into the ventricles; I suppose that procedure was done. There was a mass, in all likelihood in the neighborhood of the cerebellum and the inferior cerebellum peduncle or, possibly, in the midbrain; it could have been a pinealoma that was pressing on the brain stem. I cannot go any farther from the evidence.

Since I must make a definite diagnosis, I believe that the patient had a brain tumor, and my second choice is tuberculoma.

DR. MALLORY: There are two very definite phases to this case, the cerebral and the renal. Dr. Dahl, will you give the impression on the wards?

DR. LEWIS K. DAHL: Dr. Burnett actually followed the case. None of us suspected what was really found. I think that the most prevalent opinion on the wards was that this was periarteritis nodosa, because of the hypertension and the renal and cerebral signs.

DR. JAMES B. AYER: Is the record here? May we see the temperature chart?

DR. MALLORY: The printed record does not give any idea of the extreme elevation of temperature. On the ninth hospital day the temperature was normal, on the tenth it was 105°F., and on the morning of the eleventh it was 107°F., despite practically constant alcoholic sponges, ice packs and so forth, dropping on the following day back to 99°F. — a severe and prolonged hyperthermia.

DR. WYMAN RICHARDSON: May we see the x-ray film of the chest?

DR. JAMES R. LINGLEY: This film, taken with a portable apparatus, shows a great deal of motion. There is a small area of density, however, at the left base consistent with consolidation. This film was taken just before death.

### CLINICAL DIAGNOSES

Tuberculous meningitis?
Periarteritis nodosa?
Subacute bacterial endocarditis?
Brain tumor (pinealoma-lesion in midbrain)?
Toxic nephritis.

### DR. COHEN'S DIAGNOSIS

Brain tumor (? pinealoma).
Tuberculoma?

### ANATOMICAL DIAGNOSIS

**Pinealoma.**

### PATHOLOGICAL DISCUSSION

DR. MALLORY: I shall discuss the renal situation first and let Dr. Kubik tell us what was found in the central nervous system.

The kidneys showed a lesion that has become familiar during and since the war. There was a frank

hemoglobinuric nephrosis, with degeneration in the lower segments of the nephrons, a considerable amount of interstitial nephritis and precipitation of hemoglobin pigment in the tubules. The kidney was of the type seen with mismatched transfusion, crush syndrome, blackwater fever, burns and a number of other situations. A fairly frequent cause of such a renal injury is sulfonamide sensitivity. This man, we know, had received no sulfonamides. In the kidneys there were some questionable crystals, but on analysis in the chemistry laboratory no sulfonamides were found. The sulfonamides can therefore be completely ruled out. There had been no transfusion, no plasma and no obvious cause of hemolysis.

At the United States Army Institute of Pathology in Washington there were 120 fatal cases of heat stroke. In that group, 10 or 15 patients developed severe hemoglobinuric nephrosis and died in uremia several days after recovery from the heat stroke. In some of those cases, despite a clinical state of shock, neither whole blood nor plasma was used in treatment. Nevertheless the patients showed massive precipitation of hemoglobin in the kidneys. That is the only explanation one can find for this case. The hyperthermia was so marked that the same physiologic mechanism seen in heat stroke might easily have been involved.

DR. CHARLES L. SHORT: In artificial-fever therapy patients have been subjected to temperatures of 106.7°F. for eight hours in this hospital and in Rochester, New York, by Dr. Stafford L. Warren for thirty hours, but I remember that no cases of this syndrome were found. The patients were in reasonably good physical condition.

DR. MALLORY: The lesion is one that has been generally recognized by pathologists only within the last few years, so that I hesitate to accept a case reported over five years ago. It was probably not the hyperthermia but the subsequent shock that was responsible.

DR. CHARLES S. KUBIK: This was a tumor of the pineal region, which, I have been told, was the diagnosis made on admission by one of the house staff, who based his opinion on the defective upward conjugate movement of the eyes. This, as Dr. Cogan said in discussing another case,[2] is practically always a dependable sign of a lesion involving the quadrigeminal bodies and, in my experience, has occurred most frequently through, although not exclusively with, pinealomas and tumors in the pineal region. In this case subsequent findings and developments made the diagnosis more difficult.

On sagittal section of normal brain showing the relations of the pineal body, which is situated in the midline immediately above the superior quadrigeminal bodies and at the posterior extremity of the third ventricle just above the anterior end of the aqueduct, the pineal recess of the third ventricle actually dips into the pineal body. The spinal fluid is formed in the lateral ventricles, passes through the foramen of Monro into the third ventricle, and thence through the aqueduct into the fourth ventricle from which it enters the subarachnoid space through the foramens of Magendie and Luschka. It is readily seen why tumors in the pineal region lead to internal hydrocephalus by obstruction of the aqueduct.

In the brain in the case under discussion, behind the optic chiasm, there was a rounded prominence 1.3 cm. in diameter, which represented the floor of the third ventricle; it bulged downward because of dilatation and was also invaded by tumor. Horizontal sections of the brain showed the tumor, measuring 2.5 to 3 cm. in diameter, in the pineal region. It extended forward in the third ventricle between the optic thalami, which it invaded. It also extended downward, invading the tegmen of the midbrain and completely filling the aqueduct and the upper part of the fourth ventricle.

Anterior to the main tumor mass, the ependyma of the third ventricle and of the anterior horns of the lateral ventricles was covered with tumor implants. Implants in the third ventricle in these cases are fairly frequent and sometimes, through involvement of the hypothalamus, lead to diabetes insipidus, even when there are no clinical indications of tumor in the pineal region. There was no diabetes insipidus in this case, but the tumor involvement of the hypothalamus probably accounted for the fever.

Of the several pinealomas examined, all invaded the midbrain; none could have been removed by operation.

Histologically the tumor in this case was composed of rather large, rounded and fusiform cells with well defined cytoplasm and also of cells with poorly defined cytoplasm. An unusual feature was the presence of multinucleated cells and many giant cells, some of which had as many as twenty visible nuclei. I believe that these were tumor cells and not foreign-body giant cells.

The histologic findings were somewhat different from those observed in other cases of pinealoma, which are usually composed of fairly large rounded and polyhedral cells and are frequently infiltrated with lymphocytes and sometimes with lymphocytes and plasma cells. In the case recently discussed by Dr. Cogan[2] the tumor cells resembled very closely the cells of the normal pineal body, and there was little or no infiltration with lymphocytes.

In this case the fusiform and giant cells were unusual, but the gross findings were similar to those of pinealoma, indicating that the tumor began in the pineal region and later invaded the midbrain and optic thalami. Fusiform and giant cells are frequent in some of the gliomas, and since the parenchymal cells of the pineal body are derived from glial cells I suppose that similar de-differentiation occurs in a pinealoma.

## REFERENCES

1. Dandy, W. E. *Benign Tumors in the Third Ventricle of the Brain: Differential diagnosis and treatment.* 171 pp. Springfield, Illinois. Charles C Thomas, 1933.
2. Case records of the Massachusetts General Hospital (Case 32271). *New Eng. J. Med.* 235:25-28, 1946.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board
Joseph Garland, M.D. A. Warren Stearns, M.D.
Shields Warren, M.D. Chester S. Keefer, M.D.
C. Guy Lane, M.D. Fletcher H. Colby, M.D.
Henry R. Viets, M.D. Robert L. Goodale, M.D.
Robert M. Green, M.D. Chester M. Jones, M.D.
Charles C. Lund, M.D. Harvey R. Morrison, M.D.
Maxwell Finland, M.D.

Associate Editors
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

## "LETHEON"

The present year is one that merits more than ordinary consideration in the history of surgery and in the annals of the Massachusetts General Hospital, for it was one hundred years ago this fall, in the surgical amphitheater then under the hospital's glass-topped dome, that painless surgery was given its first public demonstration, and a new surgical era began. In 1921, with fitting ceremonies, the hospital observed its own one hundredth anniversary; on October 16, 1946, it will celebrate the centenary of its greatest single service to humanity.

The properties of sulfuric ether were far from unknown when William Thomas Green Morton, the Boston dentist, administered that volatile substance, sometime known as "Letheon," to Gilbert Abbott in order that John Collins Warren might painlessly remove a tumor from under the jaw. In the late eighteenth century there is an account of its use in a case of "pectoral catarrh," when two teaspoonfuls were volatilized and inhaled with considerable benefit to the sufferer; its employment was again reported, about the turn of the century, "for the relief of a very *painful inflammatory affection of the mamma*." We may further read, in Pereira's *Materia Medica*, published in London in 1839, that "*the vapor of ether is inhaled* in spasmodic asthma, chronic catarrh, and dyspnoea, hooping cough, and *to relieve the effects caused by the accidental inhalation of chlorine gas*."

We have Dr. Charles T. Jackson's own word for it, in a statement issued in 1847, that he had experimented with ether in 1841, and it is generally recognized that Dr. Crawford W. Long, a physician of Georgia, had used ether as a surgical anesthetic as early as 1842, although he made no public announcement of his experiences until 1849.

Sulfuric ether was not the only volatile substance whose anesthetic properties were the subject of early experimentation. Sir Humphry Davy, the noted English chemist and physicist, had investigated nitrous oxide in 1799 and suggested the use of this gas in surgical operations "attended with little effusion of blood." Horace Wells, a dentist of Hartford, formerly associated with Morton, had later experimented with the gas and had given an unsuccessful demonstration of its use in 1844. The year after ether made its debut Sir James Y. Simpson, of Edinburgh, introduced chloroform as a general anesthetic.

The recognition of anesthesia as the great turning point in surgery took place in the Massachusetts General Hospital. Its official announcement to the medical profession was made through the medium of the *Boston Medical and Surgical Journal*, on November 18, 1846, in the article "Insensibility during Surgical Operations Produced by Inhalation" by Henry Jacob Bigelow, one of the surgeons of the Massachusetts General Hospital. The *Journal* had more on the same subject in the following months, and the hospital report of 1848 announced a total of one hundred and thirty-two

operations performed within its walls using ether as an anesthetic.

The ignominious controversy that raged for a time over the credit for the ether discovery takes away nothing from the importance of the event itself. Morton wanted credit and gold, and Dr. Charles T. Jackson, whose student in chemistry he had once been, put in his claim for a major share of the honor of the discovery. The anesthetic was patented jointly by Morton and Jackson on condition of the latter that he receive one tenth of the profits, and the Board of Trustees of the hospital presented a purse of $1000 to Morton in 1848. It is not the way things are done today, and Bowditch* no doubt wrote earnestly in his history of the hospital, first published in 1851, that "the patience of the public has been long since thoroughly wearied out by the ether controversy."

The fact remains that through a long one hundred years we have had the blessing of painless surgery, with the refinements that the years have brought to it. We have had the accumulated benefit to those countless surgical patients who have found in anesthesia something like the music of the Lotos-Eaters, to wax poetical:

**Music that gentlier on the spirit lies,**
**Than tired eyelids upon tired eyes;**
**Music that brings sweet sleep down from the blissful skies.**

*Bowditch, N. I. *A History of the Massachusetts General Hospital (to August 5, 1851)*. Second edition. With a continuation to 1872 by the Reverend George E. Ellis. 34 pp. Boston: printed by the Trustees from the Bowditch Fund, 1872.

## DISABILITY FOLLOWING ACUTE HEPATITIS

THE persistence of liver damage after apparent clinical recovery from acute infectious (epidemic) hepatitis or so-called "catarrhal jaundice," has recently received a certain amount of attention.

Salmon and Richman[1] reviewed some of the recent literature on the subject and reported follow-up studies on 16 characteristic cases. They found liver damage demonstrable by the cephalin-cholesterol flocculation test and by a lowering of the diastatic activity of the serum, which persisted for a period varying from a few weeks to several months after apparent recovery from the acute attack. Others have demonstrated impairment of liver function by various tests in from 25 to over 60 per cent of patients for periods varying up to several years.

Caravati[2] noted a clinical syndrome in a number of enlisted men and officers as a sequel to homologous serum hepatitis that followed vaccination against yellow fever. The subjective symptoms of this syndrome were chronic fatigue, discomfort (a mild but constant aching) in the right upper quadrant of the abdomen, digestive disturbances (flatulent dyspepsia) especially after the ingestion of fats, malnutrition and failure to gain weight even on a high-calorie, high-vitamin diet and emotional instability. Studies of these patients revealed no hypoproteinemia, hypocalcemia or anemia, and there was no evidence of vitamin deficiency of any type. Gastric secretion and motility were found to be normal, although some showed a slight degree of hypermotility of the small intestine that was not enough to be considered significant. Studies of pancreatic function in several cases revealed no abnormality. The liver was found to be normal in size, shape and contour, and only a single patient showed evidence of liver disease, as indicated by spider angiomas over the trunk. Various liver-function tests showed no convincing evidence of residual hepatitis or of biliary-tract disease. Caravati believes that this clinical pattern is a constant finding only in such cases and that it does not follow other types of infectious hepatitis. He considers the syndrome to be an alteration of physiology caused by a mild infectious process and by an unfavorable psychic reaction to confinement by long illness. He does think, however, that the liver is probably the source of the physiologic disturbance.

Benjamin and Hoyt[3] made a study of 200 soldiers who were returned to the Lovell General Hospital because they had failed to achieve satisfactory convalescence after an attack of jaundice following yellow-fever vaccination. These cases represented only a small proportion of those who originally suffered from postvaccinal hepatitis. They had been in overseas hospitals for several months, and some of them still appeared definitely ill when they arrived, in spite of the fact that five to nine months had elapsed since their original attack of jaundice. As a group these patients were described as "pale,

thin, exhausted and utterly devoid of animation; their reactions, mental and physical, were slow and indifferent." They had had no military training whatsoever since their original illness. Their complaints were extreme weakness, overpowering fatigue, indigestion (particularly for fatty foods), anorexia, pain (especially in the right upper quadrant), nausea and vomiting, backache, insomnia, nervous irritability and tremors, and anxiety and apprehension (fear of recurrence of jaundice). From the study of these patients, Benjamin and Hoyt concluded that psychoneurotic patterns may develop as a complication of postvaccinal hepatitis or that antecedent patterns may be reborn. The bromsulfalein test for liver function showed retention of the dye in 32 per cent after twenty minutes and in 11 per cent after thirty minutes. None of the other patients had objective evidence of liver dysfunction. Improvement in damaged liver functions was still apparent at the end of six months to a year. There did not seem to be any correlation between the laboratory tests and the incidence of palpable liver edges. In 37 patients there was a vasomotor disorder, manifested by pronounced tremor, cold, red, dripping hands and overpowering weakness.

In the course of a study of acute infectious (epidemic) hepatitis in the Mediterranean Theater, Barker, Capps and Allen[4] observed that certain patients failed to recover promptly and for prolonged periods exhibited symptoms and findings that indicated persistent hepatic disease, with a tendency toward exacerbations and remissions. These cases presented a sufficiently distinctive and uniform clinical picture to justify their consideration as a separate group or syndrome, which they called "chronic hepatitis." In the 76 cases that they studied, the most characteristic and diagnostic feature was the increase in abnormal physical findings, symptoms and laboratory evidence of liver dysfunction produced by exercise. Frequently a patient appeared to have recovered while on minimal exercise, but an increase in physical activity promptly caused the clinical syndrome to reappear. They considered that the essential treatment was adequate bed rest and a high-protein diet. They made an important distinction between active and inactive hepatitis. The latter group includes patients with objective liver disease but a normal reaction to exercise. In such a situation the symptoms are not disabling, and they believe that no treatment is necessary.

**MASSACHUSETTS MEDICAL SOCIETY**
**POSTWAR LOAN FUND**

**The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:**

**George L. Schadt, *Chairman***
**Postwar Loan Fund**
**8 Fenway**
**Boston 15, Massachusetts**

In a paper recently presented at the Harvard Medical Society, Jersild described a number of cases of subacute or chronic hepatitis that occurred in Denmark during 1944–1945, when there was a widespread epidemic of infectious hepatitis similar to those that occurred in other European countries. In some of the Danish cases the disease started in the usual manner and progressed continuously, whereas in others there was definite temporary improvement, after which the disease relapsed and then progressed. The condition was associated with a high fatality rate and usually occurred in women over forty years of age. Polack[5] in 1938 described a similar but less severe condition in young adults in Copenhagen after mild attacks of infectious hepatitis.

From all these observations it appears that, although, on the whole, infectious hepatitis and homologous serum jaundice are relatively mild diseases and are associated with an extremely low mortality rate (about 0.2 per cent), cases do occur in which there is a long disabling illness with a variety of symptoms referable to the liver or nervous system or both. It also seems likely that in some of the cases of chronic hepatitis, such as those recently observed in Denmark, and in some of the cases of

homologous serum jaundice the infectious agent is one that gives rise to persistent and diffuse residual damage or to a progressive hepatic lesion oftener than does the etiologic agent associated with the usual case of infectious hepatitis or catarrhal jaundice. The implications for treatment are obvious. Patients with residual liver damage require particularly long periods of intensive dietary therapy, with avoidance of exercise beyond their tolerances.

### References


1. Salmon, G. W., and Richman, E. E. Persisting liver damage following catarrhal jaundice. *J. Pediat.* 26:533-541, 1945.
2. Caravati, C. M. Posthepatitis syndrome. *South. M. J.* 37:251-257, 1944.
3. Benjamin, J. E., and Hoyt, R. C. Disability following postvaccinal (yellow fever) hepatitis: study of 200 patients manifesting delayed convalescence. *J. A. M. A.* 128:319-324, 1945.
4. Barker, M. H., Capps, R. B., and Allen, F. W. Chronic hepatitis in Mediterranean theater: new clinical syndrome. *J. A. M. A.* 129: 653-659, 1945.
5. Polack, E. Chronic hepatitis in young persons, with or without intermittent jaundice. *Acta med. Scandinav.* 93:614-621, 1938.


## MASSACHUSETTS MEDICAL SOCIETY

### SUBCOMMITTEE ON VETERANS' AFFAIRS, POSTWAR PLANNING COMMITTEE

In March, 1946, the Subcommittee on Veterans' Affairs was appointed as a part of the Postwar Planning Committee of the Massachusetts Medical Society. This is in accordance with the sound administrative policy that limits the number of standing or special committees and provides for subcommittees of general committees for specific problems. The subcommittee, composed of five physician-veterans of World War II has met frequently, both independently and in connection with meetings of the Postwar Planning Committee.

The members of the subcommittee were pleased to find that for the past two years or more the Massachusetts Medical Society, through its officers and committees, has attempted to find solutions for the various problems that it was anticipated doctors might encounter on return from service to civilian practice. Foremost of these was judged to be that of postgraduate education and training. In addition to setting up courses of lectures and clinical demonstrations in the seven districts into which the state was divided, the committee arranged for the course of lectures held from February to May, 1946, in Sanders Theater, Cambridge. The latter course proved highly successful, with attendances at the lectures ranging from 400 to 800 physicians. Of these approximately 35 per cent were veterans, a ratio lower than had been anticipated. The second major achievement of the Postwar Planning Committee was the development of the Bureau of Clinical Information at the Headquarters of the Society, designed to serve as a clearing house for information regarding clinical lectures, ward rounds, operations and so forth that are held daily at hospitals in the Boston area. The bureau has published monthly a mimeographed schedule giving such data in detail for the convenience of veterans and other visiting physicians. The service has been used widely and has received much favorable comment. An unlooked-for development was the demand for a counseling service, which the bureau has supplied so far as its facilities have permitted. Attention should also be directed to the Loan Fund, which is available to all veterans who need it.

From the time of its organization, the Subcommittee on Veterans' Affairs has attempted to find out what other problems were of most concern to returning doctors and has tried to find solutions for such of these as were capable of solution by Society action. Information has been gained from personal interviews, from informal discussions and from questionnaires distributed at the meetings at Sanders Theater and at the annual meeting of the Society. In addition to the all-important matter of postgraduate training, including refresher courses of varying length, residencies and assistant residencies and so forth, the most frequent problems have appeared to be: suitable locations for men starting out in practice or changing place of practice from that prior to military service; availability of assistantships for men starting out in practice; hospital-staff appointments, to provide some place for hospitalization of private patients; office space and homes; telephone listings; and rebuilding of practice.

To provide readily available and up-to-date information regarding locations for practice, assistantships, opportunities in industry and so forth the subcommittee has recommended that the Bureau of Clinical Information be expanded and made a permanent installation of the Society, with sufficient personnel, both professional and secretarial, and sufficient space and funds to render this valuable service not only now but in the years to come. This has been agreed to in principle for the coming year by the appropriate authorities. Although most veteran doctors now out of the service have become settled or soon will be, it is believed that the demand for information of the sort outlined will always be great and that it is a natural function of the Massachusetts Medical Society to furnish such, even though it involves considerable expense. There are still in the service thousands of doctors, some of whom will not return to civilian life for two years or more.

The problem of hospital-staff appointments is far from easy. Hospitals in Massachusetts, in common with those all over the country, are filled to capacity constantly and have long waiting lists of patients. Doctors already on the staff have great difficulty in getting their patients in, even when the need for hospitalization is urgent. Nevertheless, the sub-

committee believes that every effort should be made by hospitals to grant staff appointments, even though of temporary nature or on the courtesy staff, to qualified doctors so that the profession will not be in the position of penalizing men for having spent from two to five years in the services. Already the president of the Massachusetts Hospital Association has sent communications to all hospitals of the Commonwealth urging that particular consideration be given to qualified veteran doctors applying for staff appointments. This supplements similar letters sent long before V-J Day by the Postwar Planning Committee to hospital superintendents, chiefs-of-staff and presidents of boards of trustees of all Massachusetts hospitals. It is earnestly hoped that all hospitals will co-operate in this important matter.

The matter of office space and homes, although acute everywhere, has not appeared to be insurmountable. It is a local problem that has almost invariably yielded to industrious search on the part of the returning veteran. Often he has not been able to secure exactly the type of office and home that he desires, but he has been able to get some type of satisfactory arrangement. The subcommittee urges that each physician having ample office space share it with a returning doctor until such time as the veteran is able to find an office for himself.

Because of the shortage of paper, telephone directories cannot be printed so often as in prewar days; consequently, some physicians will have to wait for some months before being listed. In conferences with the subcommittee, representatives of the telephone company have been most sympathetic and co-operative. The problem, however, is large and involves not only doctors but also other professional and business groups. The best solution at the moment is that returning doctors, when established, take steps to inform their patients of their new address and telephone number. The telephone company has increased its information service and states that within twenty-four hours of the installation of a telephone, the number can be secured through such service. Detailed information on this point was published in the April 18, 1946, issue of the *New England Journal of Medicine*.

The matter of rebuilding of practices and the regaining of patients is a personal, local matter. The subcommittee urges that doctors in a community take pains to inform patients acquired during the war years with the fact that their doctor has returned from the service. The subcommittee believes that no official action of the Society is appropriate in this connection.

It is of importance that all veteran physicians inform themselves on the various activities of the Society in their behalf. Many members of the Society have been in contact with younger graduates who have not yet become fellows. It is important that these young men be brought into the Society as soon as they have fulfilled the requirements. Who better can bring this before them than those members with whom they served?

* * *

All the preceding was accomplished by the work of the original small committee. At the annual meeting a group of veteran doctors held a meeting to see what further could be done for veterans. At the suggestion of this group each district was asked to appoint a representative to attend a meeting of the Subcommittee on Veterans' Affairs on June 24. At this meeting it was suggested that the original committee be enlarged to include at least one representative from each district. This was promptly accomplished, since the president of the Society was present and immediately appointed the representatives present. There was a long and free discussion of all veteran problems, from which concrete proposals emerged for further action on the part of this subcommittee. These may be briefly summarized as follows:

*Education.* It was suggested that the course at Sanders Theater be repeated (this has already been planned for) and that courses throughout the state outside of Boston be increased in number and more widely spread. It was also suggested that a two-week graduate course of intensive character be provided at some favorable spot where vacation and work could be combined — something in the nature of a medical Chatauqua. Camp Edwards was suggested as a place for such a course. (This suggestion will be submitted to the subcommittee on graduate education for consideration.)

*Automobile procurement.* It was decided to write to the larger companies to see if it is possible to secure priority for veteran physicians needing new automobiles.

*Hospital seniority.* This was discussed at some length. Contact will be made with the Massachusetts Hospital Association to discuss what steps can be taken to assure returning doctors of their former staff priority.

All agreed that the most important function of the Subcommittee was to discuss problems that confronted the medical veterans. To this end all veterans are urged to communicate any problems or suggestions that they think are worthy of study or susceptible of solution by Society action to the district representative on the committee or directly to the chairman. The list of district representatives who have been appointed appeared in the July 11 issue of the *Journal*.

G. PHILIP GRABFIELD, *Chairman*

---

## DEATH

HAYES — Frederick L. Hayes, M.D., of Brookline, died July 7. He was in his seventy-seventh year.

Dr. Hayes received his degree from Jefferson Medical College of Philadelphia in 1895. He was a fellow of the American Medical Association.

His widow survives.

(*Notices on page xxi*)

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 25

FRIDAY, JULY 26
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

TUESDAY, JULY 30
12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JULY 31
*10:30–11:30 a.m. Medical Clinic. Isolation Building, Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MARCH 15–SEPTEMBER 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

SEPTEMBER 4–7. American Congress of Physical Medicine. Page 616, issue of May 2.

SEPTEMBER 30–OCTOBER 3. Industrial Health Congress. Page 878, issue of June 27.

OCTOBER 6–12. Interamerican Congress of Cardiology. Page xix, issue of June 6.

OCTOBER 7–18. New York Academy of Medicine. Page 544, issue of April 18.

FEBRUARY 7. American Board of Obstetrics and Gynecology. Page 34, issue of July 4.

DISTRICT MEDICAL SOCIETY

PLYMOUTH

OCTOBER. Jordan Hospital, Plymouth.
NOVEMBER. Plymouth County Hospital, South Hanson.
JANUARY. Brockton Hospital, Brockton.
FEBRUARY. Moore Hospital, Brockton.
MARCH. Goddard Hospital, Brockton.
APRIL. State Farm, Bridgewater.
MAY. Lakeville Sanatorium, Lakeville.


*A Leading Economist Says:*

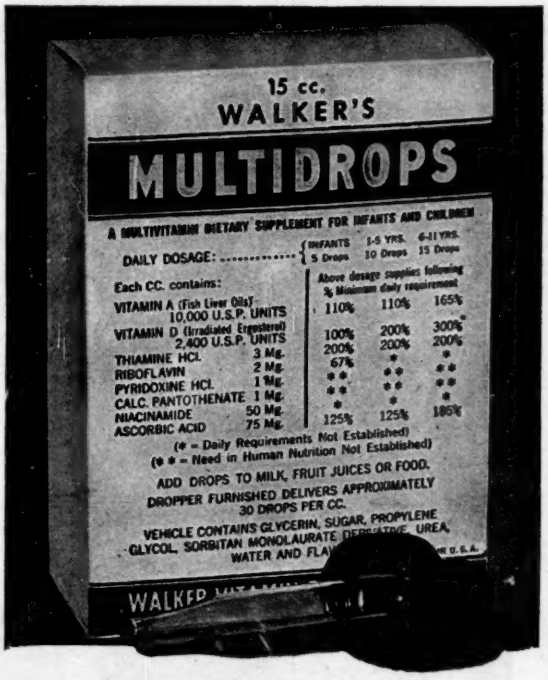
"Every successful business man today realizes that advertising is absolutely essential. Moreover, efficient advertising is an economic asset and not a waste, as some consumers seem to think. Instead of increasing prices it really has lowered them. This comes about through the economies of mass production, an American Business development that would have been impossible without advertising." — *Boston Better Business Bureau.*

**3 REASONS WHY . . .**
**FERROSATE (Kenmore)**
(Ferrous Sulfate, gr. iv.)
**Is the FERROUS SULFATE OF CHOICE**
• • • • •

1 Careful control prevents atmospheric oxidation throughout manufacture.
2 Protective sub-coating prevents premature disintegration in vivo.
3 Palatable outer sugar coating aids in preventing tooth discoloration.

Write Dept. N7 for professional sample.

**Kenmore Pharmacy, Inc.** 500 Commonwealth Ave. Boston, Mass., U.S.A.


15 cc.
WALKER'S
MULTIDROPS
A MULTIVITAMIN DIETARY SUPPLEMENT FOR INFANTS AND CHILDREN
DAILY DOSAGE:
INFANTS 5 Drops
1-5 YRS. 10 Drops
6-11 YRS. 15 Drops
Each CC. contains:
Above dosage supplies following % Minimum daily requirement
VITAMIN A (Fish Liver Oils)* 10,000 U.S.P. UNITS 110% 110% 165%
VITAMIN D (Irradiated Ergosterol) 2,400 U.S.P. UNITS 100% 200% 300%
THIAMINE HCl 3 Mg. 200% 200% 200%
RIBOFLAVIN 2 Mg. 67% * *
PYRIDOXINE HCl 1 Mg. ** ** **
CALC. PANTOTHENATE 1 Mg. ** ** **
NIACINAMIDE 50 Mg. * * *
ASCORBIC ACID 75 Mg. 125% 125% 185%
(* = Daily Requirements Not Established)
(* * = Need in Human Nutrition Not Established)
ADD DROPS TO MILK, FRUIT JUICES OR FOOD.
DROPPER FURNISHED DELIVERS APPROXIMATELY 30 DROPS PER CC.
VEHICLE CONTAINS GLYCERIN, SUGAR, PROPYLENE GLYCOL, SORBITAN MONOLAURATE, DERIVATIVE, UREA, WATER AND FLA
MADE IN U.S.A.

**CONCENTRATED EFFECTIVENESS**

A few drops, added to water, fruit juices or milk, or to the food provide ample vitamin supplementation for *infants, for children, for adults who dislike to take capsules or tablets.*

**WALKER'S**
**MULTIDROPS**

| Each cc. contains: | |
|---|---|
| Vitamin A | 10,000 I.U. |
| Vitamin D | 2,400 I.U. |
| Thiamine HCl ($B_1$) | 3 mg. |
| Riboflavin ($B_2$) | 2 mg. |
| Niacinamide | 50 mg. |
| Calcium Pantothenate | 1 mg. |
| Pyridoxine HCl ($B_6$) | 1 mg. |
| Ascorbic Acid (C) | 75 mg. |

*No fishy taste or odor*
*Convenient to handle*
*Easy to administer*

**DOSAGE:** As a daily supplement: Infants, 5-10 drops; children, 10-15 drops; adults, 15-30 drops. Therapeutic doses as determined by the physician.

**SUPPLIED:** Bottles containing 15 cc.

*Walker*
**VITAMIN PRODUCTS, INC.**
MOUNT VERNON, NEW YORK

# DEXTRI-MALTOSE
## Is Tested Bacteriologically During Every Stage

BEFORE DRYING

AFTER DRYING

WHEN PACKED

EVERY day that Dextri-Maltose is manufactured, control samples for bacteriological analyses are secured from certain points in the process which experience has shown give an accurate picture of the bacteriological condition of the product in the different steps of its manufacture. As a result of experiment and long experience, it has been demonstrated that by exercising certain strict sanitary control measures and precautions, the bacteria count can be reduced to the point where the finished product approaches practical sterility

In infant feeding the physician protects the vitality and resistance of the organism in every way possible, by using pasteurized or boiled milk, boiled water, and sterilized bottles and nipples. He therefore naturally prefers to increase this margin of safety by specifying Dextri-Maltose which is bacteriologically safe. Here where the life and health of the infant and the reputation of the physician are in the balance — VALUE, NOT PRICE, IS THE TRUE MEASURE OF ECONOMY.

**Mead Johnson & Company, Evansville, Indiana, U.S.A.**

*Eternal Vigilance Makes Dextri-Maltose Safe*

***Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.***